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Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double- blind Phase 3 trial of the EORTC Melanoma Group

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Study Coordinator: PPD

Study Chair:

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Protocol 1325-MG/ KEYNOTE 054

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DATE SIGNED	29 March 2018

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 16. 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.

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Protocol summary

Title of the Study	Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group.
Objective(s)	To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival (RFS) as compared to placebo in high-risk patients with complete resection of Stage IIIA (> 1 mm metastasis), IIIB and IIIC melanoma. To prospectively assess whether in the subgroup of patients with PD-L1-positive tumor expression, pembrolizumab improves recurrence-free survival as compared to placebo.
Methodology	This is an international, double-blinded, placebo-controlled randomized phase III trial. Enrollment will be a multi-step process. Randomization (placebo vs. pembrolizumab) will be performed centrally and will be stratified for the following factors: stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥ 4 positive lymph nodes) and region (North America, European countries, Australia and other countries as designated)). Data will be unblinded in case of recurrence and at any time during the trial in case of a safety concern affecting an individual patient.
Number of patients Number planned (Statistical design) Number analyzed	A total of approximately 900 eligible patients will be randomized into two equal-sized, double-blind treatment arms (approximately 450 patients each). The RFS final analysis will require 409 RFS events (loco-regional recurrences, distant metastases or deaths); all patients will have been followed for approximately a minimum of 1 year at approximately 3 years from the start of the trial. One interim analysis is planned for assessing whether pembrolizumab is superior to placebo with respect to the improvement of RFS in the overall population. The interim analysis will occur after approximately 330 RFS events have been reported, and will be based on the primary efficacy analysis on the primary efficacy population (ITT population). The stopping boundaries for the interim analysis will be based on the O'Brien-Fleming spending function. The Distant metastases-free survival (DMFS) final analysis will require 423 DMFS events (distant metastases or deaths); it will be done approximately 5 years from the trial inception.

The OS final analysis will require 380 deaths; it will be done approximately 8-8.5 years from the trial inception.

The "graphical approach" to testing the hypotheses that the Pembrolizumab and placebo groups differ with respect to RFS, RFS in the PD-L1+ subgroup, DMFS, and DMFS in the PD-L1+ subgroup, OS, OS in the PD-L1+ subgroup, will be adopted.

Objective	HR	1-sided alpha %†	Power %
RFS in the overall population	0.7	2.5 (1.4)	95 (92)
RFS in the PD-L1+ subgroup (if 205/409 events are PD-L1+)	0.55	2.5 (1.54)	99 (98)
	0.60	2.5 (1.54)	95 (93)
DMFS in the overall population (if both RFS null hypotheses are rejected)	0.725	2.5 (1.4)	91 (87)
DMFS in the PD-L1+ subgroup (if both RFS null hypotheses are rejected and if 212/423 events are PD-L1+)	0.55	2.5 (1.54)	99 (99)
	0.60	2.5 (1.54)	99 (94)
OS (if both DMFS and both RFSs null hypotheses are rejected)	0.75	2.5 (1.4)	80 (73)
OS in the PD-L1+ subgroup (if both RFSs and both DMFS null hypotheses are rejected and if 190/380 of events are PD-L1+)	0.65	2.5 (1.54)	84 (79)
	0.7	2.5 (1.54)	69 (62)

† According to the multiplicity strategy (Bonferroni-Holm), the hypothesis for the overall population will first be tested at alpha=1.4%. If the hypothesis for the PD-L1+ subgroup is rejected at the allocated alpha (alpha in parentheses), then the hypothesis for the overall population will be tested at alpha=2.5%. Similarly, the hypothesis for the PD-L1+ subgroup will first be tested at the allocated alpha (alpha in parentheses). If the hypothesis for the overall population is rejected at alpha=1.4% (alpha in parentheses), then the hypothesis for the PD-L1+ subgroup will be tested at

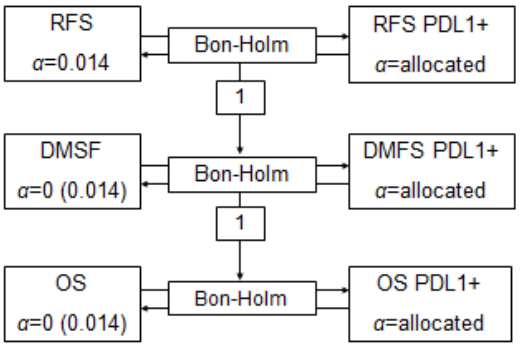
alpha=2.5%.

The "graphical approach" (see Figure 5 below) to testing the hypotheses that the Pembrolizumab and placebo groups differ with respect to RFS, DMFS, OS and these endpoints in the PD-L1+ subgroup, will be adopted.

The initial 1-sided alpha allocation to RFS, DMFS and OS, will be 0.025, 0 and 0, respectively. This indicates that RFS, DMFS and OS will be tested sequentially. Both hypotheses (for the overall population and for the PD-L1+ subgroup) must be rejected to proceed to the next endpoint.

For each endpoint, alpha allocation was determined as follows. For the overall population, 1-sided alpha=0.014. For the PD-L1+ subgroup, the allocated alpha will be calculated as a function of the event ratio (number of observed events in the PD-L1+ subgroup: total number of observed events) using a method by Spiessens and Debois. Several scenarios are discussed in the sample size calculation (above).

This "graphical approach" guarantees a 1-sided significance level of 0.025 for the study, as a whole. No multiplicity adjustment for other secondary analyses will be made.



Bretz, F., Maurer, W., Brannath, W. and Posch, M. (2009), A graphical approach to sequentially rejective multiple test procedures. *Statist Med* 2009, 28: 586–604.

Spiessens and Debois. Adjusted significance levels for subgroup analysis in clinical trials. *Cont Clin Trials* 2010; 31: 647–656.

Figure 5: Graphical approach

At the time of OS final analysis, an assessment of the long term treatment impact on RFS and DMFS will be evaluated as well.

Diagnosis and main criteria for inclusion	Patient enrollment will follow a three steps procedure as illustrated in Section 4 (step 1 registration, step 2 central confirmation of PD-L1 expression, step 3 enrollment and randomization through IVRS). Patients must meet all of the criteria described in Section 3 to be eligible for enrollment . **1) Registration- step 1 (ORTA Step 1)** **Before patient registration, written informed consent for tumor testing must be given according to ICH/GCP, and national/local regulations.** **Note: if a patient signs the Registration Informed Consent before the complete lymph node dissection (CLND) was performed, please contact the medical monitor to assess eligibility before registering in ORTA.** ♦ At least 18 years of age. ♦ No mucosal or ocular melanoma. ♦ Melanoma with unknown origin of the primary is eligible. ♦ Complete resection of Stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as (AJCC, 2010): Stage IIIA with metastasis > 1 mm; any Stage IIIB or IIIC. No past or current in-transit metastases or satellitosis. ♦ Patient population IIIA (> 1 mm metastasis) is capped at a maximum of 20% of the total patient population. ♦ Mandatory to ship tumor sample for evaluation of PD-L1 expression. A tumor sample obtained at resection or tissue obtained from the biopsy must not be previously irradiated. During the screening period, the tumor sample must be sent to the central pathology laboratory for PD-L1 expression testing. Patients will be eligible to participate regardless of the level of PD-L1 expression. ♦ PD-L1 testing is mandatory: tumor material will be collected from positive lymph nodes (LN) embedded in paraffin. If the resection samples from LNs are not adequate for PD-L1 testing, the primary melanoma must be collected. Patients whose samples are inadequate for PD-L1 determination will not be enrolled. ♦ In addition the primary melanoma may also be collected if available to evaluate the PD-L1 expression. **2) Central confirmation of PD-L1 expression - step 2** This central confirmation through EORTC is required for enrolling the patient in step 3.

	3) Enrollment and randomization -step 3 (ORTA Step 2) **Before patient enrollment, written informed consent to participate in the trial must be given according to ICH/GCP, and national/local regulations**. ♦ The resection of Stage III lymph nodes must have been performed in complete compliance with the Criteria for adequate surgical procedures for CLND that is displayed in Appendix F. This must be documented in the medical file (including pathology report); patients without documentation of adequate resection are not eligible. ♦ To be considered as adequate, the surgical and pathological procedures should have included at least the following: ♦ Head and Neck ♦ Minimum of 15 pathologically investigated nodes ♦ Face, ear, and anterior scalp: parotidectomy plus modified radical neck dissection ♦ Posterior scalp: modified radical neck dissection plus suboccipital nodes. For this specific localization, a CLND will be considered as adequate if at least 5 LN have been investigated ♦ Upper Extremity ♦ Minimum of 10 pathologically investigated nodes ♦ Axillary node dissection included at least 10 nodes taken from Levels I and II ♦ Level III nodes dissected if they were clinically involved ♦ Pectoralis minor muscle may be divided or sacrificed with the specimen at the discretion of the surgeon ♦ Lower Extremity ♦ Minimum of 5 pathologically investigated nodes ♦ Superficial inguinal node dissection was performed for non-palpable nodal involvement ♦ If Cloquet's node was positive, a deep inguinal node dissection was performed ♦ Lymph Node Dissection for Nodal Recurrence ♦ Regional node recurrence was treated using the appropriate lymphadenectomy as above ♦ Diagnosis of regional node recurrence was made by fine needle aspiration technique to avoid contaminating the

region with tumor, followed by CLND as above

- The maximum duration from surgery to first study drug treatment is 13 weeks. Treatment should start only after complete wound healing from the surgery.

  Note: if there is a delay of 1-7 days exceeding 13 weeks due to extreme unforeseen circumstances, the eligibility should be discussed with the medical monitor.

- Disease status for the post-surgery baseline assessment must be documented by full Chest/Abdomen/Pelvis CT and/or MRI with Neck CT and/or MRI (for Head and Neck primaries) and complete clinical examination after the informed consent and prior to enrollment.

  Note: if a patient had laboratory/imaging tests as part of local routine guidelines (standard of care) prior to signing informed consent, the procedures will be acceptable for screening purposes if they are within the window required by the protocol.

- Disease-free (no loco-regional relapse or distant metastasis); no clinical evidence for brain metastases.
- BRAF mutation status (known or not done).
- ECOG performance status of 0 or 1.
- Patient demonstrates adequate organ function as defined in Table 2, all screening labs should be performed within 14 days (+/- 3 days) prior to treatment initiation.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /mcL
Platelets	≥ 100,000 / mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Creatinine or Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl) Creatinine clearance should be calculated per institutional standard.	≤ 1.5xULN or ≥ 60 mL/min for patient with creatinine levels > 1.5x institutional ULN Note: For patients entering Part 2 ≥ 30 mL/min for patient with creatinine levels > 1.5x institutional

	ULN
Hepatic	
Total bilirubin	≤ 1.5xULN or Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5xULN
AST (SGOT) and ALT (SGPT)	≤ 2.5xULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5xULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤ 1.5xULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Table 2: Adequate Organ Function Laboratory Values

- Prior treatment for melanoma
  - In case of an indication for post lymph node dissection radiotherapy, this must have been completed within the 13 weeks post-surgery period and prior to treatment start.

    Note: radiotherapy may alter the process of wound healing. If the wound healing is not complete patient will not be eligible.
  - No prior therapy for melanoma except surgery for primary melanoma lesions; patients who have previously received IFN for thick primary melanomas without evidence of lymph node involvement are eligible.
- No history of (non-infectious) pneumonitis that required steroids or current pneumonitis. No history of or current interstitial lung disease.
- No history of another malignancy or a concurrent malignancy. Exceptions include patients who have been disease-free for 5 years, or patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible, for example cervical cancer in situ.
- No active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents,

	corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. ♦ No active infection requiring therapy. ♦ Patients with hyperthyroidism or hypothyroidism but that are stable on hormone replacement will not be excluded. ♦ No diagnosis of immunodeficiency, no systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment ♦ No known history of human immunodeficiency virus (HIV), active Hepatitis B or Hepatitis C. ♦ Patients who received treatment with live vaccines within 30 days prior to the first dose of study medication are not eligible. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, seasonal flu, H1N1 flu, rabies, BCG and typhoid vaccine. ♦ Patient must not have received prior treatment with any anti-CTLA4 monoclonal antibody or anti-PD-1, or PD-L1 or PD-L2 agent. Examples of PD-1 inhibitors (include, but are not limited to): pembrolizumab (Merck); Nivolumab (also known as BMS-936558, MDX-1106, ONO-4538) (Bristol-Myers Squibb); Pidilizumab (CT-11) (Cure-Tech/Teva); and AMP-224 (Amplimmune). Examples of PD-L1 inhibitors (include, but are not limited to): BMS-936559 (also known as MDX-1105) (Bristol-Myers Squibb); MPDL3280A (also known as RG7446) (Roche Genentech); and MEDI4736 (MedImmune). ♦ Patient is not currently participating and receiving study therapy or has not participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks prior to the first dose of treatment ♦ Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment. ♦ Patients of childbearing / reproductive potential should use adequate birth control methods, as defined by the investigator, during the study treatment period and for a period of 120 days after the last dose of study drug. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly. ♦ Note: abstinence is acceptable if this is established and preferred

	contraception for the patient and is accepted as a local standard. ♦ Appendix N is to be used where applicable for specific countries and sites adhering to Clinical Trial Facilitation Group guidelines for clinical trials (e.g. United Kingdom, Norway, Sweden, Portugal, etc). ♦ Female patients who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 120 days after the last dose of study drug . ♦ Absence of any condition hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial. ♦ Patient will not be eligible: if patient is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) 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. **Once eligibility has been verified, the treatment arm will be randomly allocated to the patient.** **Important note: All eligibility criteria must be adhered to.**
Treatment Test product, dose and mode of administration	1) Adjuvant therapy: Pembrolizumab 200 mg fixed dose OR Placebo, will be administered by IV, every 3 weeks. 2) After 1st recurrence: Upon documented recurrence patients are eligible for cross-over/re-challenge and if patients fulfill criteria as per Sections 4.2.1.1 (cross-over) and 4.2.2.1 (re-challenge) : a) Patients assigned to the placebo adjuvant arm who experience disease recurrence may be treated with pembrolizumab 200 mg IV every 3 weeks if clinically indicated. b) Patients assigned to the pembrolizumab adjuvant arm who experience disease recurrence more than six months after completing one year of therapy may be re- challenged with pembrolizumab 200 mg IV every 3 weeks if clinically indicated.
Duration of treatment	1) Adjuvant treatment: Study drugs will be administered for 1 year unless one of the withdrawal criteria applies (Section 5.4.1.2) 2) After 1st recurrence: Treatment in Part 2 will be administered up to 1 year (local recurrence) or 2 years treatment period unless occurrence of a withdrawal criterion

	(see Section 5.4.2.4). For patients with local recurrence, the treatment may stop at 1 year at the discretion of the investigator.
Reference therapy, dose and mode of administration	1) Adjuvant therapy Placebo will be administered by IV, every 3 weeks. 2) After 1st recurrence: Upon documented recurrence, eligible patients will be offered to receive pembrolizumab at 200 mg fixed dose, administered by IV, every 3 weeks if they fulfill criteria as per Section 4.2.1.1
Criteria for evaluation	
Efficacy	Primary endpoint: ♦ Recurrence-free survival (RFS) ♦ RFS for patients with PD-L1-positive expression Secondary endpoints: ♦ Distant metastases-free survival (DMFS) ♦ DMFS for patients with PD-L1-positive expression ♦ Overall survival (OS) ♦ OS for patients with PD-L1-positive expression ♦ Pharmacokinetics (PK) of pembrolizumab
Safety Exploratory	Adverse events will be scored according to the CTCAE version 4.0 ♦ Quality of life ♦ Health outcomes evaluation ♦ Predictive biomarkers (e.g. immune-related gene signatures, genetic variation, SPDL1) for treatment difference in outcome ♦ Progression/recurrence-free survival 2 (PRFS2)
Statistical methods	All the main analyses of the efficacy endpoints (RFS, DMFS, OS) will be performed on the intent-to-treat (ITT) population using the ITT principle: patients will be considered in the treatment group as indicated at randomization, regardless the "treatment" duration, cause of going off-protocol treatment, possible switch to another treatment before the 1st relapse, etc. The Kaplan-Meier technique will be used to obtain estimates of the survival-type distributions (RFS, DMFS, OS), and the standard error of the estimates will be computed using the Greenwood formula. Medians - if reached - will be presented with a 95% confidence interval based on

	the non-parametric method of Brookmeyer and Crowley. The comparison of the time-to-event distributions (RFS, DMFS, OS) between the two treatment arms will be done using the log-rank test stratified by stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 nodes vs. IIIc ≥4 nodes) as indicated at randomization. The HR, and its 2-sided (1-alpha)*100% confidence interval, of Pembrolizumab to placebo, will be estimated using a Cox proportional hazards (PH) model (using Efron's tie-handling method), stratified by stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 nodes vs. IIIc ≥4 nodes) as indicated at randomization, with treatment as the single covariate. Predictive importance of a factor i.e. its impact on the treatment difference regarding the time to event end point (RFS, DMFS, OS) will be investigated for exploratory purposes. Consistency of treatment comparisons among subgroups of variables will be investigated using the Forest plot techniques. In addition, possible interactions between a factor and treatment effect will be assessed in a Cox model, in a bi-variate setting (i.e. treatment, variable, treatment x variable) and a multivariate one, i.e. adding in the model those factors which appear to be of independent prognostic importance. The prognostic/predictive importance of the following variables will be considered for the efficacy endpoints (RFS, DMFS, OS): ♦ PD-L1 expression (negative vs positive). ♦ Variables considered in the AJCC Staging: ♦ LN involvement: micro vs. macro- involvement ♦ Ulceration: absent vs. present vs. unknown ♦ Number of lymph-nodes positive: 1 vs. 2-3 vs. 4+ ♦ Breslow thickness (< 2 mm vs 2-<4 mm vs ≥4 mm) ♦ BRAF-mutation status (negative vs positive vs unknown) ♦ Sex (Male vs. Female) ♦ Age (at randomization <65 vs. ≥65 yrs) For efficacy endpoints, several sensitivity analyses are foreseen (see protocol, Section 8.2.4.1).

Pharmaco-kinetic and pharmaco-dynamic evaluations	To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned. For sampling refer to Sections 6.2.5, 6.3.3, 6.3.4.5 and 6.4.3. **If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical trials, it may be decided to discontinue further sample collection or analysis in this study.**
Translational research	Tumor material, blood and serum samples will be collected for future research. For sampling refer to Sections 6.2.2, 6.3.4.4 and 6.4.3.
Quality of Life	HRQoL is an exploratory endpoint testing the hypothesis of no clinically relevant differences between the two treatment arms using the global QoL scale during the first two years. To meet this objective, the QLQ-C30 (v3) and the EQ-5D-3L will be administered at baseline and every 12 weeks for the first two years and every 6 months up to 4th year (included), regardless of recurrence/progression or treatment status, unless patient withdraws from this part of the study.

1 Background and introduction

1.1 Disease background information

1.1.1 Risk of relapse in patients with stage III melanoma

The increase in incidence of melanoma has led to an increased number of patients with regional positive lymph nodes (stage III) being diagnosed each year, across the globe, but especially in the western world (Ref. 1). Breslow thickness of primary melanoma is the strongest prognostic factor in terms of likelihood of micrometastatic disease at the regional lymph node level. Likelihood of systemic metastatic disease in patients with regional lymph node metastasis (stage III) correlates closely with microscopic vs palpable nodal disease and with number of positive nodes. Stage III melanoma patients are at high risk of relapse. According to the data of the most recent AJCC staging committee relapse rates at 5 years for Stage IIIA, Stage IIIB and Stage IIIC are about 35%, 75% and 90% respectively (Ref. 2, Ref. 3). Because of sentinel node (SN) staging there is tremendous heterogeneity within the sentinel node positive (microscopic only) patient population. Depending on tumor load in the sentinel node defined by diameter of the micrometastasis(es) according to the Rotterdam Criteria, prognosis rapidly deteriorates from equal to a sentinel node negative status in case of metastasis < 0.1 mm to equal to having 1 palpable positive node in case of metastasis > 1 mm (Ref. 4, Ref. 5, Ref. 6). Patients with a metastasis > 1 mm have a highly significant higher risk of relapse and death than patients with a metastasis < 1 mm (Ref. 6).

In the conduct of adjuvant trials in stage III disease, it is important to be able to have a timely read out of the impact of the drug on relapse- free survival (RFS) and overall survival (OS) and to be able to achieve that goal one should not dilute the stage III patient population by including the very large numbers of SN-positive patients with metastasis < 1 mm, but one should enrich the patient population in the study by only enrolling patients with a high risk (stage IIIA, > 1 mm diameter of metastasis) or with multiple microscopically positive nodes or palpable nodes (stage IIIB and IIIC).

There is a large unmet medical need in patients with resectable advanced stage IIIA (>1 mm metastasis), IIIB and IIIC melanoma, who are at high-risk of disease recurrence because of the marginal impact of adjuvant IFN regimens on OS as will be discussed in Section 1.1.3.1.1 of the protocol.

1.1.2 Surgical management of regional lymph nodes

Patients with operable clinically positive nodes undergo systematically full lymphadenectomy of the involved sites. Patients with clinically negative lymph node involvement are most commonly staged by sentinel lymph node biopsy, which has replaced the former use of elective lymph node dissection (Ref. 7).

Patients with a negative sentinel lymph node are spared a complete lymph node dissection (CLND), whereas patients with a positive SN most commonly undergo a CLND (Ref. 7, Ref. 8). CLND may not be indicated for all patients, but differentiation regarding the indication for CLND is a topic under current investigation (Ref. 9). In the context of an adjuvant trial in stage III patients, enriched for risk of relapse, it is recommended that all

patients have undergone full regional lymph node dissection to avoid heterogeneity and risk of early locoregional relapses because of not having had optimal surgery for optimal locoregional control, as has been practiced in the most recent EORTC phase III trials (EORTC-18991 and 18071) in stage III (Ref. 10).

1.1.3 Adjuvant Therapy in high risk melanoma patients

1.1.3.1 Adjuvant trials

Surgery alone is insufficient to achieve a cure in most patients with stage III melanoma. Thus systemic adjuvant therapy has been investigated over the last decades in patients with high risk (Tany N1,2,3 M0: microscopically or clinically node- positive patients). Up to now, adjuvant therapy of stage III malignant melanoma with cytostatic agents and/or nonspecific immunotherapy, biologic response modifiers and combinations have failed to show a clear clinical benefit especially in terms of survival (Ref. 1).

1.1.3.1.1 Interferon-α trials

Adjuvant Therapy with Interferon

Twenty-five years of RCTs in melanoma with interferon-alpha (IFN) are a testimony that efficacy of adjuvant therapy with IFN is modest at best. High-dose interferon-α is approved in the USA and EU for the treatment of patients with completely resected Stage IIB/ III melanoma.

Many other dose regimens have been tested over the years. Meta-analyses of phase III trials demonstrated that IFN has a consistent effect on RFS but no or only a marginal effect on OS (Ref. 11, Ref. 12, Ref. 13). No relationship between dose or duration of treatment with outcome has been demonstrated. These findings suggest that only a minority of patients are sensitive to IFN and demands that we identify these patients. Based on the EORTC 18991 trial in 1256 patients, the FDA approved pegylated interferon α-2b (Peg-IFN; Sylatron™) in 2011 for stage III melanoma patients (Ref. 14) . The EORTC 18952 trial in 1388 stage IIB/III melanoma patients, compared intermediate doses of interferon α-2b (IFN) with observation (Ref. 15). These EORTC RCTs stratified patients by SN-staging (microscopic involvement only: stage III-N1) or gross macroscopic relapse (stage III-N2) as well as by presence or absence of ulceration in the primary tumor. Both stage and ulceration are key prognostic factors (Ref. 2, Ref. 3). Patients with only micrometastases have a much better prognosis than patients with palpable node metastases (Ref. 2, Ref. 3). Palpable nodal disease may represent more aggressive disease from the onset or by acquisition of additional mutations over time. Regarding ulceration, for the same Breslow thickness, patients with an ulcerated primary have a 10-25% lower survival probability at 10 years, indicating a distinct biologic entity (Ref. 2).

The meta-analysis of the two largest adjuvant IFN/PEG-IFN RCTs in 2644 patients demonstrated that both tumor load in the lymph nodes and ulceration of the primary are independent predictive factors for adjuvant IFN therapy (Ref. 16). Patients with favorable stage (IIb/III-N1) and/or ulcerated primary tumor benefited significantly from IFN/PEG-IFN treatment (HRs 0.56–0.69) with regard to RFS, distant metastasis free survival (DMFS), and OS, whereas patients with stage III-N2 disease or non-ulcerated primary tumor did not.

Ulceration of the primary was the overridingly important predictive factor for IFN-sensitivity, which was again confirmed at 7.6 years follow up of EORTC 18991 (Ref. 17).

In a meta-analysis of 1393 patients with ulcerated melanomas reported in a variety of trials that did not include EORTC 18991, Wheatley et al. reported a HR of adjuvant IFN therapy for OS of 0.77 (99% CI 0.63–0.93); whilst there was no impact of adjuvant IFN therapy in the 2118 patients without ulceration (HR 0.98 [99% CI 0.87–1.17]) (Ref. 16).

In 2012, the results of the adjuvant phase III trial of adjuvant biochemotherapy (CVD + IL2 + IFN) demonstrated a significant improvement on RFS but no improvement of OS. These results are interesting but not practice changing (Ref. 18).

1.1.3.2 Adjuvant trial with anti-CTLA-4 monoclonal antibody ipilimumab

In 2014, at the annual meeting of ASCO the EORTC18071 trial results for the primary endpoint RFS were reported. EORTC 18071 evaluates in patients with advanced stage III melanoma (stage IIIA > 1 mm diameter; stage IIIB/IIIC), in a double-blind RCT the impact of adjuvant ipilimumab versus placebo in 951 patients (EORTC 18071; ClinicalTrials.gov, number NCT00636168) (Ref. 19). The results indicated a significant impact on RFS (HR 0.75; p=0.002). Median RFS was 17 months in the placebo arm versus 26 months in the ipilimmab treated patients. Data on DMFS and OS were not mature and therefore not reported. Adverse Events (AE) were quite frequent. Most common grade 3/4 immune-related adverse events (irAEs) in the ipilimumab and placebo arms were gastrointestinal (15.9% vs 0.8%), hepatic (10.6% vs 0.2%), and endocrine (8.5% vs 0%). Most irAEs were managed and resolved using established algorithms. Of 471 patients who started ipilimumab, 245 (52%) discontinued treatment due to AEs [182 (38.6%) within 12 weeks]. Five patients (1.1%) died due to drug-related AEs. The trial is being continued for DMFS and OS reporting in the next few years.

1.1.3.3 Summary of rationale for observation as comparator

While high dose interferon is approved by the EMA, the current standard of care for locally advanced melanoma remains controversial. This uncertainty is reflected in current National Comprehensive Cancer Network (NCCN) guidelines, which support observation as one approach to patient management in this setting. Uncertainty about the clinical utility of interferon, together with a potential reluctance to expose patients who may be cured by surgery alone to potentially toxic regimens, has led many physicians in European countries to accept surgery alone as a standard of care for locally advanced melanoma. Observation was used as a comparator in the recent EORTC 18991 and 18071 trials.

1.2 Rationale for trial proposal

1.2.1 Immunotherapy and melanoma

Immunologic interventions to treat cancer can potentially be achieved through the induction of an immune response (active immunotherapy), administration of antibodies (passive immunotherapy), and/or stimulation of effector cells with cytokines or antibodies. All of these approaches have been investigated in melanoma and have shown early promise. Immune-modulating agents such as IFN-α and interleukin-2 (IL-2) have shown efficacy

against melanoma and have been approved by the FDA for the treatment of various stages of melanoma. In addition to a direct cytotoxic effect, IFN-α is able to stimulate natural killer (NK) cell activity and to regulate the expression of histocompatibility antigens or tumor-associated antigens and demonstrate a 10-15% response rate in metastatic melanoma with less than 5% complete responses. The median duration of response ranged from 6 - 12 months. IFN-α treatment, however, is associated with significant toxicity.

IL-2 modulates the immune system by stimulating the growth and activity of T lymphocytes, human lymphocyte antigen (HLA)-restricted or -non- restricted cytotoxic T cells and induces the production of many cytokines, such as tumor necrosis factor (TNF), IFN- α and IL-1. IL-2 is currently approved in the USA for treatment of Stage IV melanoma; however, its usage is also limited due to its significant toxicities. Various combinations of IL-2, IFN- α, and chemotherapy drugs have failed to significantly improve survival or quality of life.

1.2.2 Immunomodulation and breaking immune tolerance

1.2.2.1 Recent developments with anti-CTLA4 and Anti-PD1/PDL1 immune checkpoint blockers

Tackling immune suppression, seems to be a much more powerful intervention than short-lived immune-activating strategies and the current axioma of "Inhibiting the inhibitor" and ''breaking tolerance'' appears to be a particularly powerful approach. This was first demonstrated by the success of anti-CTLA4 molecules, resulting in the approval of ipilimumab for patients with advanced melanoma in 2011 (Ref. 20, Ref. 21), with similar results reported for renal cell cancer as early as in 2005 by the group of Steve Rosenberg at the NCI Surgery Branch (Ref. 22). It was observed that long lasting responses seem to depend on immunologic control and are rarely obtained with chemotherapy or targeted therapies alone. Although BRAF and MEK-inhibitors alone produce responses in up to 50% of patients with a BRAF-mutated melanoma, these responses are in general only short lived responses lasting 5-6 months (Ref. 23, Ref. 24, Ref. 25). Combinations of these targeted agents indicate additive effects, but resistance seems to occur in most patients and tumor control seems still only temporary (Ref. 26).

1.2.2.2 Durability of response: hall mark of immune checkpoint blockers

In contrast to the response rates with these targeted agents in BRAF-mutated melanomas, response rates with ipilimumab in melanoma (mutated and non-mutated) patients are lower (10-15%), but of high durability of about 1.5-2 years (Ref. 20, Ref. 21). Large data sets have now confirmed that immunotherapy with ipilimumab is associated with 2-5 year survival rates in previously treated advanced melanoma patients to be close to 20% and in treatment naïve patients to be superior to 30% (Ref. 27).

The efficacy indicators of the anti-PD-1 molecules nivolumab and pembrolizumab (MK-3475 and previously lambrolizumab) appear quite superior those of ipilimumab. Response rates are significantly higher and range from 30-50%, while importantly the responses are similarly durable, if not superior to the durability of ipilimumab ones (Ref. 28, Ref. 29, Ref. 30). Moreover the toxicity profile is much more favorable than that of ipilimumab. At the annual meeting of the American Society for Clinical Oncology (ASCO) in 2013 the long term follow up data of patients treated with nivolumab were reported and showed

unprecedented 61% one-year and 44% 2-year survival rates (Ref. 29) and were confirmed by the update in 2014 at ASCO (Ref. 31).

Anti-PD1 monoclonal antibodies seem to combine the best of both worlds i.e. high response rates and durable responses. The largest study that has been reported on anti-PD1 activity in patients with advanced melanoma pertain to pembrolizumab. Initial results were reported in 2013 (Ref. 32) and in 2014 at the annual meeting of ASCO the results in 411 patients were reported (Ref. 33). High response rates and great durability of responses were confirmed in the experience with 411 patients. The overall response rate (ORR) by RECIST was 40% (95% CI 32%-48%) in ipilimumab-naive (IPI-N) and 28% (95% CI 22%-35%) in ipilimumab - treated (IPI-T) patients. Responses were durable (88% ongoing at analysis). Median PFS by RECIST was 24 weeks in IPI-N and 23 weeks in IPI-T patients. Median OS was not reached, with 1-y OS of 71% in all patients. Benefit was observed by both RECIST and irRC at all doses and schedules in IPI-N and IPI-T patients. Pembrolizumab demonstrated activity in all major subgroups irrespective of ECOG PS, LDH levels, BRAF mutation, M stage, and number and type of prior therapy. Overall, 12% of patients experienced drug-related grade 3/4 AEs and only 4% of patients discontinued due to a drug-related AE. There were no drug-related deaths.

1.2.2.2.1 Combinations

The first data in 53 patients, indicate that ipilimumab and nivolumab can be used in combination and improve response rates even further (Ref. 34, Ref. 35). With a 62% dose limiting toxicity rate however, this combination may not be suited for use in the adjuvant setting (Ref. 34).

All these results clearly indicate that a new era for immunotherapy has arrived and that tumor control and “clinical cure” are now real phenomena in the context of the observation that most of the patients with durable responses seem to have obtained a state of tumor control rather than one of complete tumor eradication.

1.2.3 Background data for anti-PD-1 and PD-L1

The programmed death receptor 1 (PD-1) is another key immune checkpoint receptor expressed by activated T cells. 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 immunoglobulin (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 (Ref. 36, Ref. 37). The structure of murine PD-1 has been resolved (Ref. 38). Not only tumor cells can suppress activated-T-Cell function by expressing PD-1 receptor ligand, but also (and importantly) myeloid cells in the tumor-infiltrate.

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 responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains two 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 CD3, PKCθ, and ZAP70, which are involved in the CD3 T cell signaling cascade (Ref. 37, Ref. 39, Ref. 40, Ref. 41).

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 (Ref. 42, Ref. 43). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T cells, B cells, T regs, and natural killer cells (Ref. 44, Ref. 45). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells, as well as subsets of macrophages and dendritic cells (Ref. 46).

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 and in various tumors (Ref. 43, Ref. 47, Ref. 48, Ref. 49, Ref. 50). Both ligands are type 1 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-L1 or PD-L2 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 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 (Ref. 43). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (Ref. 51), pancreatic carcinoma (Ref. 52), hepatocellular carcinoma (Ref. 53), and ovarian carcinoma (Ref. 54). Furthermore, PD-1 has been suggested to regulate tumor-specific T cell expansion in patients with melanoma (Ref. 55, Ref. 57).

1.2.4 Pembrolizumab characteristics and clinical data overview

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and 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 being advanced for clinical development as an IV immunotherapy for advanced malignancies.

1.2.4.1 Non-Clinical Toxicology Summary of Results

In the 1-month and 6-month toxicology study in cynomologus monkeys, pembrolizumab administered once a week and once every other week respectively, intravenously up to 200 mg/kg resulted in no adverse treatment related effects. The exposure multiple based on a predicted $AUC_{0\text{-}tau}$ of 4464 µg.day/mL at the maximum anticipated human clinical dose of 10 mg/kg (every 2 weeks) Q2W or Q3W (every 3 weeks) is 15-fold at 200 mg/kg, the NOAEL for the 6-month monkey study. Additionally, in the tissue cross-reactivity study of pembrolizumab with human and monkey tissues demonstrated the expected on-target

staining of the membranes of mononuclear leukocytes in both species. Off-target cross-reactivity staining was also noted in both species but was limited to cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to the experimental method artifacts, i.e. tissue processing for IHC, that are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

No reproductive or developmental toxicity studies are planned with pembrolizumab. Therefore, inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

1.2.4.2 Clinical development

As of September 03, 2016, about 21,036 subjects have been treated with pembrolizumab at several dose schedules. Pembrolizumab has been generally well tolerated, as expected based on preclinical findings and other anti-PD-1 monoclonal antibodies.

Merck is studying pembrolizumab for various oncology indications (Ref. 56). These studies are further outlined in the Investigator's Brochure.

1.2.4.2.1 Initial pembrolizumab clinical development

An open-label Phase I study (Protocol 001) is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this study evaluated three dose levels of single agent pembrolizumab (1 mg/kg, 3 mg/kg, and 10 mg/kg), in patients with progressive locally advanced or metastatic carcinoma, melanoma [IPI-naïve or previously treated with IPI], and non-small cell lung carcinoma (NSCLC). As of 26-Jul-2013, there have been 789 patients treated with pembrolizumab as a 30-minute IV infusion. Of these 789 patients, preliminary data are available from 479 patients. Based upon this safety database consisting of patients treated up to 10 mg/kg once every two to three weeks, pembrolizumab has been generally well-tolerated at doses up to 10 mg/kg every other week without DLTs. No serious infusions reactions have been reported. One (0.002%) patient assayed to date had samples confirmed positive for ADA, but no impact on safety has been observed.Pembrolizumab pharmacokinetic results have been obtained following the first dose at 1, 3 and 10 mg/kg IV of pembrolizumab administered to 17 patients with solid tumors. The observed pharmacokinetic profile of pembrolizumab was typical of other IgG mAbs with a half-life (t½) of approximately 2 to 3 weeks. There was no indication of dose dependency of half-life in the 3 dose groups and a dose related increase in exposure was observed from 1 to 10 mg/kg. The long half-life supports a dosing interval of every 2 or 3 weeks. Exposure obtained with sparse sampling after dosing melanoma and NSCLC patients at 2 and 10 mg/kg, every 2 or 3 weeks, is consistent with this profile.
Pembrolizumab monotherapy induced an ORR of 25%/27% in patients with ipilimumab-exposed melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. Pembrolizumab monotherapy induced an ORR of 39%/43% in patients with ipilimumab-naive melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. These responses are remarkably durable. The

preliminary 1-year survival rate for patients, many of whom have had multiple therapies, including ipilimumab, who receive pembrolizumab is 81%.

The most commonly reported treatment emergent AEs experienced are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhoea (22.3%) and rash (21.5%). irAEs were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported, irAEs across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhoea (2.2%), and pneumonitis (1.9%).

The organ most frequently affected by irAEs with pembrolizumab is the skin. Less frequently affected tissues include thyroid gland, colon, lung, kidney, and liver.

Review of the overall benefit:risk ratio of pembrolizumab favors enrollment of eligible patients into clinical trials of pembrolizumab. The preliminary data suggest that a dose of pembrolizumab at 2 mg/kg every 3weeks is appropriate for patients with melanoma. Fixed dosing at 200 mg every three weeks will be discussed in Section 5.2.1.

1.2.4.2.2 Pembrolizumab melanoma clinical trials

Results from a phase II registration trial (MK-3475 PN 002) comparing two doses of pembrolizumab versus investigator choice of standard chemotherapy in patients with advanced melanoma who have progressed after prior therapy (clinicaltrials.gov identifier NCT10704287) were reported at the Society for Melanoma Research in November, 2014 (Ref. 67). The primary objectives were to evaluate progression free survival (PFS) or OS of pembrolizumab versus standard of care chemotherapy. Pembrolizumab substantially increased PFS at 6 months from 16% to 36% (HR = 0.53 [C.I. 0.43, 0.65]). Assessment of OS was immature, and will be further evaluated at later analyses. Incidence of treatment-related AEs was lower in the pembrolizumab arms compared with the chemotherapy arm.

Results from a Phase III registration trial (MK-3475-006 AM1) of pembrolizumab versus ipilimumab in ipilimumab-naive patients with advanced melanoma were recently published after the trial closed early due to demonstrated efficacy of pembrolizumab over ipilimumab (Ref. 68). This was a 3-arm study to evaluate the safety and efficacy of two dosing schedules of pembrolizumab compared to ipilimumab for the treatment of ipilimumab-naïve participants with unresectable or metastatic melanoma. Patients were randomized to receive pembrolizumab 10 mg/kg every 2 weeks for up to 2 years or pembrolizumab 10 mg/kg every 3 weeks for up to 2 years or ipilimumab 3 mg/kg for a total of 4 doses. Primary endpoints of this study are PFS and OS. The estimated 6-month PFS rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (HR for disease progression, 0.58; P<0.001 for both pembrolizumab regimens versus ipilimumab). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively (HR for death for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 to 0.83; P = 0.0005; HR for pembrolizumab every 3 weeks, 0.69; 95% CI, 0.52 to 0.90; P = 0.0036).

Additional studies of pembrolizumab in advanced melanoma are ongoing. MK-3475 027 is evaluating efficacy and safety of pembrolizumab in melanoma and NSCLC metastatic to brain. MK-3475 022 is evaluating safety and efficacy of pembrolizumab in combination with the mutant BRAF inhibitors Trametinib and Dabrafenib. Safety and efficacy of combinations with ipilimumab and peg-interferon will be evaluated in MK-3475 029. MK-3475-034 is

evaluating the safety and efficacy of pembrolizumab in combination with talimogene laherperpvec. MK-3475-053 is comparing Investigator's choice of high dose interferon or ipilimumab to pembrolizumab. MK-3475-252 is evaluating the efficacy of pembrolizumab in combination with epacadostat or placebo. For these and other ongoing trial details please refer to the Investigator's brochure (IB).

1.2.4.2.3 Relationship of response to pembrolizumab depends on PD-L1 expression as evaluated by immunohistochemistry

Expression of PD-L1 has been shown to be associated with tumor response and survival in the initial phase 1 trial KEYNOTE-001 (NCT01295827) presented at ASCO in 2014 by PPD Tumor response in 125 patients treated with any of the three weight-based regimens was assessed by RECIST 1.1 and compared to PD-L1 tumor expression in pretreatment biopsy specimens. Tumor PD-L1 expression was assessed by IHC and a ≥1% expression in stained cells was used to define the positive population. Tumor PD-L1 expression levels were associated with tumor response (Table 1). While there was a general association of response with PD-L1 positive status, PD-L1 negative patients responded and their responses were as durable as those of the PD-L1 positive patients.

	10 mg/kg Q2W n = 35	10 mg/kg Q3W n = 47	2 mg/kg Q3W n = 31
PD-L1+ *	86%	77%	55%
Overall response rate			
Unselected	51%	32%	39%
PD-L1 +	57%	39%	59%
PD-L1-	20%	9%	14%

*Level of PD-L1 expression in percentage

Table 1: Overall response rate by PD-L1 positivity by dose and schedule

Overall and progression free survival were evaluated as well (Figure 1). It is important to again note that a longer PFS was generally associated with PD-L1 positivity, PD-L1 negative patients had prolonged benefit, and the overall survival of the PD-L1 negative patients was prolonged and has not crossed the median after longer than one year.

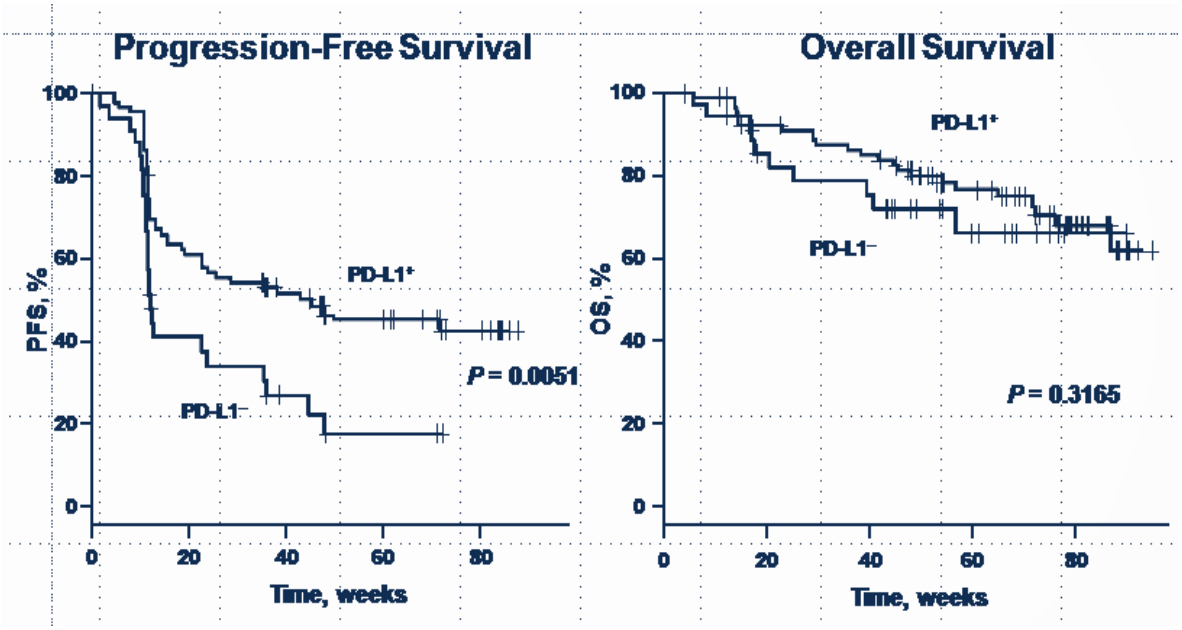


Figure 1: PFS and OS based on tumor PD-L1 expression (Central Review, RECIST v.1.1)

Given the evidence that both PD-L1 positive and negative patients can benefit from pembrolizumab in the metastatic setting, this study will evaluate potential benefit in both the overall population, as well as the PD-L1 positive biomarker subgroup.

1.2.4.2.4 Pembrolizumab clinical trials in non-melanoma indications

Additional clinical trials are being conducted in NSCLC, head and neck cancer, triple negative breast cancer, gastric cancer, bladder cancer, hematologic malignancies and a range of additional malignancies. For additional trial details please refer to the IB.

A randomized, adaptively designed Phase II/III trial (Protocol 010) is being conducted to evaluate two dosing schedules of pembrolizumab (10 mg/kg Q3W or 2 mg/kg Q3W) versus docetaxel in previously treated patients with NSCLC with PD-L1 positive tumors who have experienced disease progression after platinum-containing systemic therapy. This protocol has randomized three patients with NSCLC across the 3 treatment groups: 10 mg/kg Q3W, 2 mg/kg Q3W, and docetaxel 75 mg/m² Q3W in a 1:1:1 ratio. No safety and efficacy data are available. Two phase III registration trials studies of first line therapy with pembrolizumab are designed as pivotal tests of its efficacy in NSCLC (MK-3475 024 and 042).

A non-randomized, multi-cohort trial (Protocol 012) is evaluating pembrolizumab 10 mg/kg Q2W in patients with PD-L1 positive advanced solid tumors. Cohort A has enrolled patients with triple negative breast cancer, Cohort B has enrolled patients with squamous cell carcinoma of the head and neck, Cohort C has enrolled patients with urothelial tract cancer of the renal pelvis, ureter, bladder, or urethra. Cohort D has enrolled patients with adenocarcinoma of the stomach or gastroesophageal junction. Safety and efficacy of pembrolizumab are being evaluated in an additional 20 tumor indications in MK-3475 028.

2 Objectives of the trial

2.1 Primary objective

- To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival, as compared to placebo in high-risk patients with complete resection of Stage IIIA (>1 mm metastasis), IIIB and IIIC melanoma.
- To prospectively assess whether in the subgroup of patients with PD-L1-positive tumor expression, pembrolizumab improves recurrence-free survival as compared to placebo.

2.2 Secondary objectives

- To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves distant metastasis free survival as compared to placebo.
- To prospectively assess whether in the subgroup of patients with PD-L1-positive tumor expression pembrolizumab improves distant metastasis free survival as compared to placebo.
- To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves overall survival, as compared to placebo.
- To prospectively assess whether in the subgroup of patients with PD-L1-positive tumor expression pembrolizumab improves overall survival as compared to placebo.
- To compare adverse event profiles (AE and Serious Adverse Event (SAE)) between patients receiving pembrolizumab versus patients in the placebo arm.
- To evaluate the pharmacokinetics (PK) of pembrolizumab when pembrolizumab is administered at 200 mg every three weeks.

2.3 Exploratory objectives

- To compare quality of life between the two arms (pembrolizumab versus placebo).
- To compare health outcomes evaluation between the two arms (pembrolizumab versus placebo).
- To evaluate predictive biomarkers (e.g., immune-related gene signatures, genetic variation, SPDL1) for treatment difference in outcome.
- Progression/recurrence-free survival 2 (PRFS2)

2.4 End-points

Refer to Section 7 for definitions of endpoints

2.4.1 Primary endpoint

The primary endpoints are:

- Recurrence free survival (RFS)
- RFS in subgroup of patients with PD-L1-positive tumor expression receiving either pembrolizumab or placebo

2.4.2 Secondary endpoints

- Distant metastases-free survival (DMFS)
- DMFS in subgroup of patients with PD-L1-positive tumor expression receiving either pembrolizumab or placebo
- Overall survival (OS)
- OS in subgroup of patients with PD-L1-positive tumor expression receiving either pembrolizumab or placebo
- Toxicity profile according to Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0
- To evaluate the pharmacokinetics (PK) of pembrolizumab when pembrolizumab is administered 200 mg every 3 weeks
- To assess for development of anti-drug antibodies (ADA)

2.4.3 Exploratory endpoints

- Quality of life
- Health outcomes evaluation
- To evaluate predictive biomarkers (e.g. immune-related gene signatures, genetic variation, SPDL1) for treatment difference in outcome
- Progression/recurrence-free survival 2 (PRFS2)

3 Patient selection criteria

Patient enrollment will follow a three steps procedure as illustrated in Section 4 (step 1 registration, step 2 central confirmation of PD-L1 expression, step 3 enrollment and randomization through IVRS). Patients must meet all of the criteria described in Section 3 to be eligible for enrollment.

3.1 Registration- step 1 (ORTA Step 1)

Before patient registration, written informed consent for tumor testing must be given according to ICH/GCP, and national/local regulations.

Note: if a patient signs the Registration Informed Consent before CLND was performed, please contact the medical monitor to assess eligibility before registering in ORTA.

- At least 18 years of age.
- No mucosal or ocular melanoma.
- Melanoma with unknown origin of the primary is eligible.
- Complete resection of Stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as (AJCC, 2010): Stage IIIA with metastasis > 1 mm; any Stage IIIB or IIIC. No past or current in-transit metastases or satellitosis.
  - Patient population IIIA (> 1 mm metastasis) is capped at a maximum of 20% of the total patient population.
- Mandatory to ship tumor sample for evaluation of PD-L1 expression. A tumor sample obtained at resection or tissue obtained from the biopsy must not be previously irradiated. During the screening period, the tumor sample must be sent to the central pathology laboratory for PD-L1 expression testing. Patients will be eligible to participate regardless of the level of PD-L1 expression.
  - PD-L1 testing is mandatory: tumor material will be collected from positive lymph nodes (LN) embedded in paraffin. If the resection samples from LNs are not adequate for PD-L1 testing, the primary melanoma must be collected. Patients whose samples are inadequate for PD-L1 determination will not be enrolled.
  - In addition the primary melanoma may also be collected if available to evaluate the PD-L1 expression.

3.2 Central confirmation of PD-L1 expression - step 2

This central confirmation through EORTC is required for enrolling the patient in step 3

3.3 Enrollment and Randomization - step 3 (ORTA Step 2)

Before patient enrollment, written informed consent to participate in the trial must be given according to ICH/GCP, and national/local regulations.

- The resection of Stage III lymph nodes must have been performed in complete compliance with the Criteria for adequate surgical procedures for complete lymph node dissection (CLND) that is displayed in Appendix F. This must be documented in the medical file (including the pathology report); patients without documentation of adequate resection are not eligible.
- To be considered as adequate, the surgical and pathological procedures should have included at least the following:
  - Head and Neck
    - Minimum of 15 pathologically investigated nodes
    - Face, ear, and anterior scalp: parotidectomy plus modified radical neck dissection
    - Posterior scalp: modified radical neck dissection plus suboccipital nodes. For this specific localization, a CLND will be considered as adequate if at least 5 LN have been investigated

- Upper Extremity
  - Minimum of 10 pathologically investigated nodes
  - Axillary node dissection included at least 10 nodes taken from Levels I and II
  - Level III nodes dissected if they were clinically involved
  - Pectoralis minor muscle may be divided or sacrificed with the specimen at the discretion of the surgeon
- Lower Extremity
  - Minimum of 5 pathologically investigated nodes
  - Superficial inguinal node dissection was performed for non-palpable nodal involvement
  - If Cloquet's node was positive, a deep inguinal node dissection was performed
- Lymph Node Dissection for Nodal Recurrence
  - Regional node recurrence was treated using the appropriate lymphadenectomy as above
  - Diagnosis of regional node recurrence was made by fine needle aspiration technique to avoid contaminating the region with tumor, followed by CLND as above

- The maximum duration from surgery to first study drug treatment is 13 weeks. Treatment should start only after complete wound healing from the surgery.

  Note: if there is a delay of 1-7 days exceeding 13 weeks due to extreme unforeseen circumstances, the eligibility should be discussed with the medical monitor.

- Disease status for the post-surgery baseline assessment must be documented by full Chest/Abdomen/Pelvis CT and/or MRI with Neck CT and/or MRI (for Head and Neck primaries) and complete clinical examination after the informed consent and prior to enrollment.

  Note: if a patient had laboratory/imaging tests as part of local routine guidelines (standard of care) prior to signing informed consent, the procedures will be acceptable for screening purposes if they are within the window required by the protocol.

- Disease-free (no loco-regional relapse or distant metastasis); no clinical evidence for brain metastases.
- BRAF mutation status (known or not done).
- ECOG performance status of 0 or 1.

Patient demonstrates adequate organ function as defined in Table 2, screening labs should be performed within 14 days (+/- 3 days) prior to treatment initiation.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /mcL
Platelets	≥ 100,000 / mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Creatinine or Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl) Creatinine clearance should be calculated per institutional standard.	≤ 1.5xULN or ≥ 60 mL/min for patient with creatinine levels > 1.5x institutional ULN Note: For patients entering Part 2 ≥ 30 mL/min for patient with creatinine levels > 1.5x institutional ULN
Hepatic	
Total bilirubin	≤ 1.5xULN or Direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤ 2.5xULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5xULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤ 1.5xULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Table 2: Adequate Organ Function Laboratory ValuesPrior treatment for melanoma

- In case of an indication for post lymph node dissection radiotherapy, this must have been completed within the 13 weeks post-surgery period and prior to treatment start.

  Note: radiotherapy may alter the process of wound healing. If the wound healing is not complete patient will not be eligible.

- No prior therapy for melanoma except surgery for primary melanoma lesions; patients who have previously received IFN for thick primary melanomas without evidence of lymph node involvement are eligible.

- No history of (non-infectious) pneumonitis that required steroids or current pneumonitis. No history of or current interstitial lung disease.
- No history of another malignancy or a concurrent malignancy. Exceptions include patients who have been disease-free for 5 years, or patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible, for example cervical cancer in situ.
- No active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- No active infection requiring therapy.
- Patients with hyperthyroidism or hypothyroidism but that are stable on hormone replacement will not be excluded.
- No diagnosis of immunodeficiency, no systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
- No known history of human immunodeficiency virus (HIV), active Hepatitis B or Hepatitis C.
- Patients who received treatment with live vaccines within 30 days prior to the first dose of study medication are not eligible. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, seasonal flu, H1N1 flu, rabies, BCG and typhoid vaccine.
- Patient must not have received prior treatment with any anti-CTLA4 monoclonal antibody or anti-PD-1, or PD-L1 or PD-L2 agent.

Examples of PD-1 inhibitors (include, but are not limited to): pembrolizumab (Merck); Nivolumab (also known as BMS-936558, MDX-1106, ONO-4538) (Bristol-Myers Squibb); Pidilizumab (CT-11) (Cure-Tech/Teva); and AMP-224 (Amplimmune).

Examples of PD-L1 inhibitors (include, but are not limited to): BMS-936559 (also known as MDX-1105) (Bristol-Myers Squibb); MPDL3280A (also known as RG7446) (Roche Genentech); and MEDI4736 (MedImmune).

- Patient is not currently participating and receiving study therapy or has not participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks prior to the first dose of treatment
- Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment.
- Patients of childbearing / reproductive potential should use adequate birth control methods, as defined by the investigator, during the study treatment period and for a

period of 120 days after the last dose study drug. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.

- Note: abstinence is acceptable if this is established and preferred contraception for the patient and is accepted as a local standard.
- Please refer to Appendix N for recommendations based on Clinical Trial Facilitation Group guidelines for sites and countries where applicable (e.g. United Kingdom, Norway, Sweden, Portugal, etc).

- Female patients who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 120 days after the last dose of study drug.
- Absence of any condition hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
- Patient will not be eligible: if patient is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) 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.

Once eligibility has been verified, the treatment arm will be randomly allocated to the patient.

Important note: All eligibility criteria must be adhered to.

4 Trial Design

This is an international, double-blinded, placebo-controlled randomized phase III trial. The trial design is detailed in Figure 3.

4.1 Part 1: Adjuvant therapy

4.1.1 Multi step process for enrollment

Patients will enter the screening phase to assess their eligibility after complete resection of stage III melanoma.

The surgery date is defined as the latest surgery that made the patient free of disease (AJCC R0).

4.1.1.1 Registration - step 1 (ORTA Step 1)

Upon consent, patient will be registered and a sample of the resected tumor material will be evaluated for PD-L1 expression at a central pathology lab.

Evaluation of response in PD-L1 biomarker populations: Section 1.2.4.2.3 describes the potential correlation of patient response with the expression status of PD-L1 in their tumor. All patients will be required to submit a sample of their resected tumor for PD-L1 IHC expression for evaluation by a vendor designated by the Sponsor. Tumor material will be evaluated by the central laboratory following procedures outlined in the Procedures manual. Results will be recorded as positive (≥ 1% PD-L1 IHC), negative (< 1% PD-L1 IHC) or undetermined level of expression (indeterminate PD-L1 IHC) for subgroup analysis.

Biological material for PD-L1 testing: tumor material will be collected from positive lymph nodes. Lymph nodes embedded in paraffin will be stained with anti-PD-L1 antibodies.

If PD-L1 status cannot be determined from the lymph node samples, then primary melanoma will be screened for PD-L1 expression. Primary melanoma samples may be substituted for the lymph node tissues as needed.

4.1.1.2 Central confirmation of PD-L1 expression- step 2

Confirmation of PD-L1 status by the central laboratory through EORTC.

4.1.1.3 Enrollment and Randomization - step 3 (ORTA Step 2)

The confirmation of PD-L1 expression must be available before proceeding with the enrollment in the study. The patient's written informed consent to undergo screening for the clinical trial must be given prior to the performance of any protocol laboratory/imaging tests that are not part of local routine guidelines.

Once eligibility has been verified, the treatment arm will be randomly allocated to the patient (see Figure 2).

Note: if after randomization patient develops an adverse event, it has to resolve to Grade 0-1 before dosing. If the delay exceeds the 13 weeks interval from surgery to start of treatment, please contact the medical monitor.

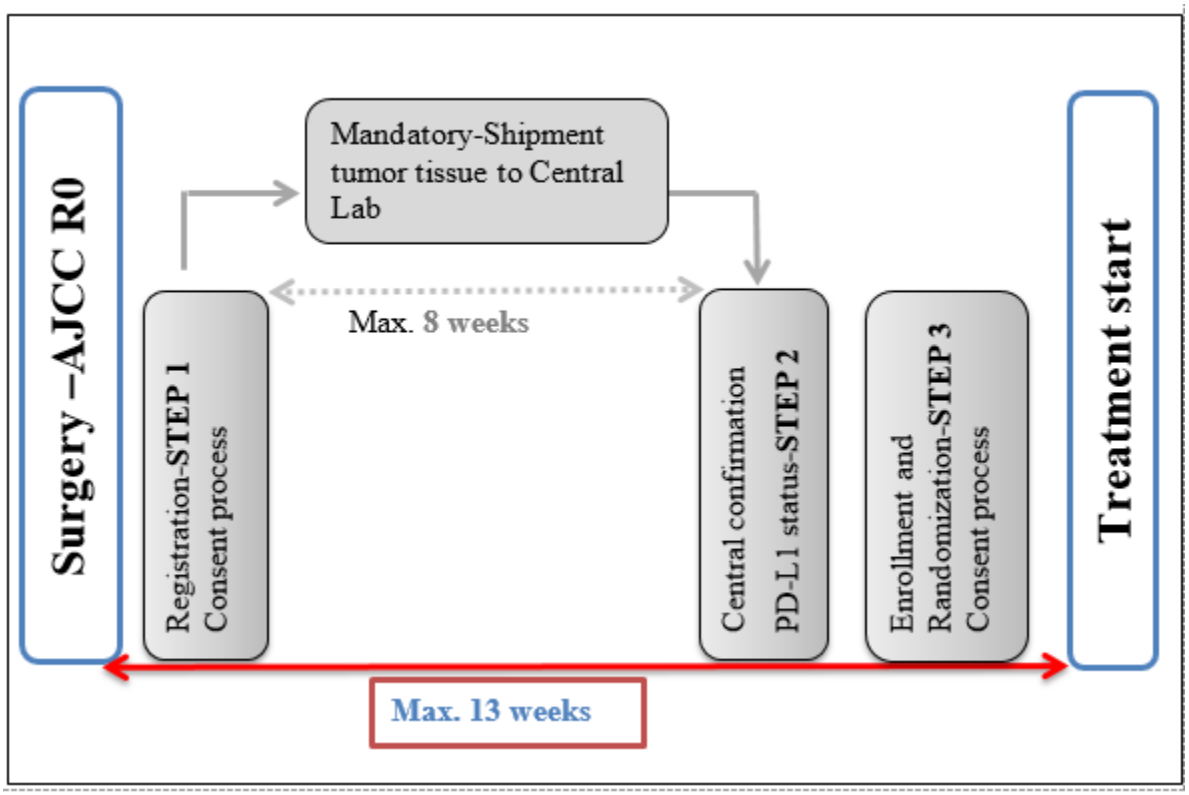


Figure 2. Multi step process for enrollment

4.1.2 Sample size and stratification factors

A total of approximately 900 eligible patients will be randomized into two equal-sized double blind treatment arms (approximately 450 patients each) to receive pembrolizumab vs placebo.

The treatment should start no later than 13 weeks after surgery and only after complete wound healing from the surgery.

Randomization will be performed centrally (see Section 14) and will be stratified for the following factors:

- Stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes)
- Region (North America, European countries, Australia and other countries as designated)

4.2 Part 2: after the first recurrence (Cross-over or Re-challenge treatment)

The main inclusion criteria previously established for Part 1 remains for Part 2 of the study except for the below:

- Surgery, biopsy and/or radiotherapy (palliative or adjuvant) are allowed prior to Part 2. Radiotherapy has to be completed prior to first dose and complete wound healing is required prior to first dose.
- Latest imaging scan date should be within 4 weeks (+/- 7 days) prior to first dose.
- All lab assessments described in Table 2 should be performed within 14 days (+/- 3 days) prior to first dose.

  Note: For patients entering Part 2, creatinine clearance ≥ 30 mL/min for patient with creatinine levels > 1.5x institutional ULN
- All other assessements (physical exam, AE/Conmeds, QoLs, etc) are to be performed within 14 days (+/- 3 days) prior to first dose

IMPORTANT: Patients enrolled in Part 2 of the study (Cross-over or Re-challenge treatment) should not receive any other form of antineoplastic or adjuvant therapy.

4.2.1 Crossover for patients in the placebo arm with documented recurrence

Patients assigned to the placebo arm who experience disease recurrence (as per Section 7.1.1) and meet all crossover criteria (Section 4.2.1.1), will be offered to crossover to pembrolizumab and receive pembrolizumab 200 mg IV Q3W.

The primary objective of the overall study is to compare RFS of pembrolizumab versus placebo, while ensuring access to pembrolizumab for all patients entering the study by allowing crossover after recurrence.

4.2.1.1 Crossover qualifications

Patients will be considered for crossover to pembrolizumab after documented recurrence as per Section 7.1.1. Crossover is optional and is at the discretion of the Investigator. Patients who meet the following criteria are eligible for crossover:

- No evidence of brain metastases or any other central nervous system (CNS) disease (e.g, leptomeningeal disease, spinal cord, etc.). An imaging scan is required to confirm no brain metastasis or other CNS.

  Note : a brain MRI is required to confirm absence of brain metastasis and leptomeningeal disease. Additional imaging should be obtained as indicated in symptomatic patients.
- **After the first recurrence, if patient experiences a second recurrence or a progression before enrolment in part 2, he/she will not be eligible for part 2.**
- ECOG performance status 0-2
- Documentation of recurrence as per Section 7.1.1

- Consent for the cross-over and collection of tumor material. For patients who will have a biopsy to confirm the recurrence or for those that will undergo surgery, they will be asked to consent to assess the PD-L1 status using the newly collected tumor material and to biobank this tumor material.

Note: the results from PD-L1 testing for Part 2 are not needed prior to treatment start.

4.2.1.2 Crossover Assessments and Procedures

All procedures and assessments completed at the time of withdrawal from adjuvant treatment may be used as appropriate for the start of the Crossover part of the study.

4.2.2 Rechallenge for patients in the pembrolizumab arm with documented recurrence >6 months after completion of one year of adjuvant therapy

4.2.2.1 Rechallenge qualifications

Patients will be considered for re-treatment with pembrolizumab after documented recurrence if their disease recurs > 6 months after completing one year of adjuvant pembrolizumab treatment as per Section 7.1.1. Re-challenge is optional and is at the discretion of the Investigator. Patients who meet the following criteria are eligible for re-challenge:

- No evidence of brain metastases or any other central nervous system (CNS) disease (e.g, leptomeningeal disease, spinal cord, etc.). An imaging scan is required to confirm no brain metastasis or other CNS.

  Note : a brain MRI is required to confirm absence of brain metastasis and leptomeningeal disease. Additional imaging should be obtained as indicated in symptomatic patients.

- **After the first recurrence, if patient experiences a second recurrence or a progression before enrolment in part 2, he/she will not be eligible for part 2.**
- ECOG performance status 0-2
- Documentation of recurrence as per Section 7.1.1
- Consent for the rechallenge
- Collection of tumor material. Patients who will have a biopsy to confirm the recurrence or patients that will undergo surgery will be asked to consent to assess tumor PD-L1 status using newly collected tumor material and to biobank this tumor material.

Note: the results from PD-L1 testing for Part 2 are not needed prior to treatment start.

4.2.2.2 Rechallenge Assessments and Procedures

All procedures and assessments completed at the time of withdrawal from adjuvant treatment may be used as appropriate for the start of the re-challenge part of the study.

4.3 Unblinding data

The authorized unblinding of treatment arm will take place under the following conditions:

- Emergency unblinding
- Unblinding by investigator after first disease recurrence
- Unblinding at final analysis
- Other unblinding during the course of the study

Please see Section 14.7 for unblinding procedures

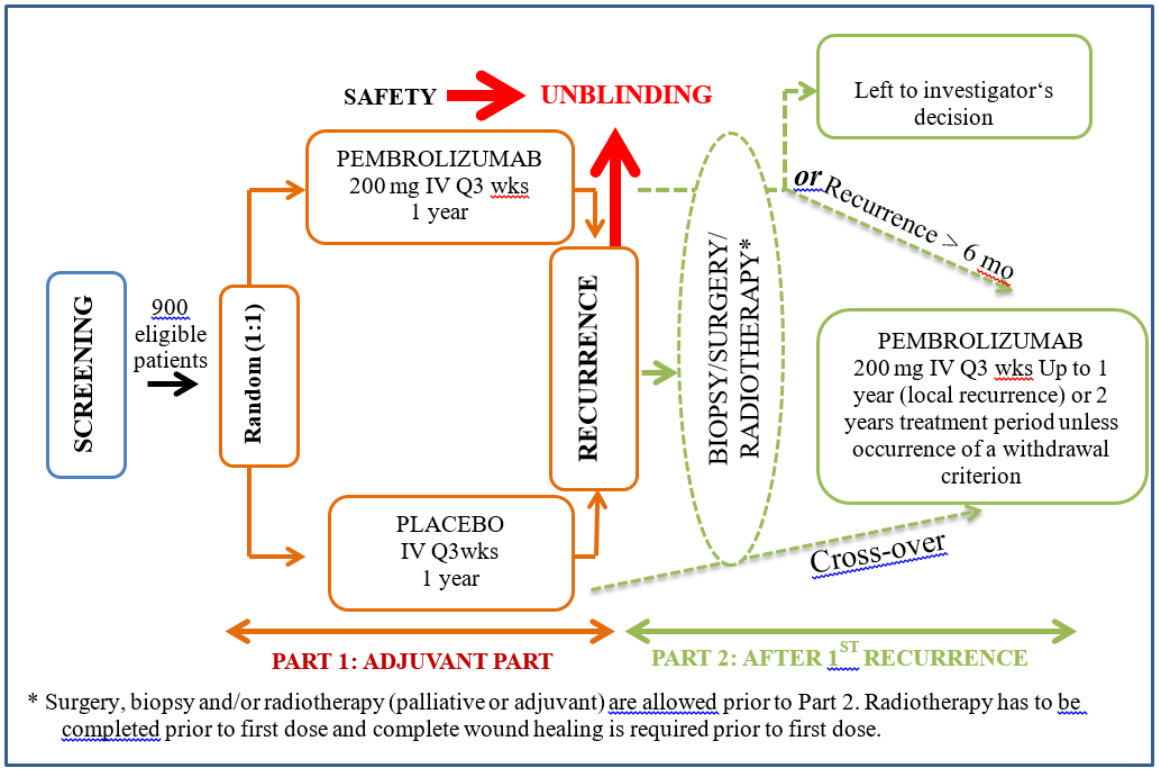


Figure 3: Trial design

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Placebo

Placebo will be normal saline solution prepared by the local pharmacist, dosed and administered in the same manner as the investigational product.

5.2 Pembrolizumab (MK-3475)

The nomenclature of pembrolizumab drug substance

Code name: MK-3475 (Anti-PD-1)

Chemical name: Humanized X PD-1_mAb (H409A11) IgG4

5.2.1 Selected dose

PK data analysis of pembrolizumab administered Q2W and 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 provided a scientific rationale for evaluating the Q3W dosing schedule.

The choice of the 200 mg Q3W as an appropriate dose for fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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 PK data obtained in this study as well as PK data obtained from other studies (if available), a population PK analysis will be performed to characterize pharmacokinetic parameters (Cmax, AUC, Ctrough) as endpoints and evaluate the effect of extrinsic and intrinsic factors to support the proposed dosing regimen. Pharmacokinetic samples will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

5.3 Drug supply

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.

5.3.1 Placebo

Placebo for this trial will be provided by investigational sites and prepared by the local unblinded pharmacist.

5.3.2 Pembrolizumab

Pembrolizumab will be provided by Merck.

5.3.2.1 Initial drug supply

Refer to Pharmacy manual.

5.3.2.2 Drug resupply by IVRS

Refer to IVRS manual.

5.3.3 Packaging, labeling, handling and storage

5.3.3.1 Packaging

Packaging and labeling of Pembrolizumab will be in accordance with Good Manufacturing Practice (GMP) for clinical trials.

5.3.3.2 Labeling

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

5.3.3.3 Dosage and Administration

Pembrolizumab will be provided by Merck in vials of 50 mg lyophilized powder or in 100 mg liquid vials.

Details on the dose preparation and administration are provided in the Unblinded Pharmacist Manual.

5.3.3.4 Storage

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The Investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light and humidity) as determined by the Sponsor and defined on the label.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

5.3.4 Drug accountability

The unblinded pharmacist is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the unblinded pharmacist or designated site staff must maintain investigational product accountability records throughout the course of the study. This person(s) will document the amount of investigational product dispensed and/or administered to study patients and the amount received from and returned to Merck, when applicable.

5.3.5 Return of investigational product

The unblinded pharmacist is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to the patients 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.

5.3.6 Destruction of investigational product

The unblinded pharmacist is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to the patients 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, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented. Unused clinical supplies can only be destroyed after being inspected and reconciled by the responsible study monitor.

5.3.7 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS system) to allocate patients, to assign treatment to patients 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.

5.4 Treatment schedule

The treatment schedule is detailed in Figure 4.

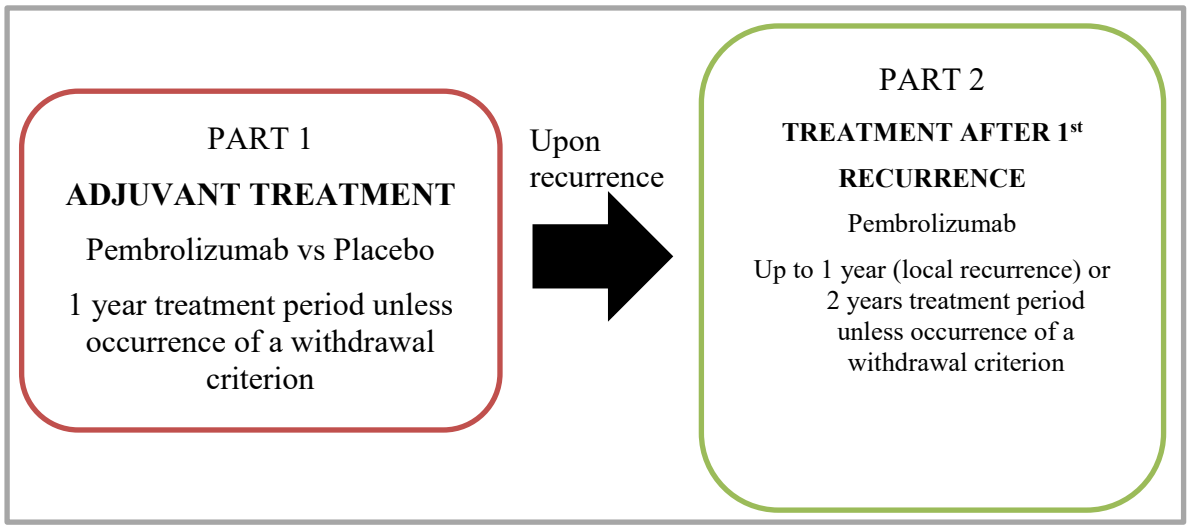


Figure 4: Treatment schedule

5.4.1 Part 1: Adjuvant therapy schedule, duration and withdrawal

Pembrolizumab 200 mg fixed dose OR Placebo 0 mg, will be administered by IV, every 3 weeks (+/- 3 days).

5.4.1.1 Adjuvant treatment duration

Pembrolizumab/Placebo will be administered intravenously (IV), every 3 weeks, for 1 year or to complete total 18 doses.

Note: if cycles are skipped and/or delayed treatment will continue beyond 1 year in order to complete the 18 doses. For any patient who is not able to complete the required 18 doses, a notification to the study monitor is required to determine if it would impact eligibility for entry into Part 2.

5.4.1.2 Withdrawal criteria for Part 1 adjuvant treatment

Patients may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice.

The following conditions require patient discontinuation from study treatment:

- Recurrence as defined in Section 7.1.1. Upon recurrence, the treatment will be unblinded
- Normal completion of the protocol treatment (one year)
  - Note: one year of treatment is calculated from the date of first dose
- AE or intercurrent illness that, in the opinion of the investigator, warrants the patient's withdrawal from study treatment.

- Specific conditions described in the Management of Adverse Events (see Appendix G and Appendix H).
- Investigator's decision to withdraw the patient
- Noncompliance with study treatment or procedure requirements
    - Lost to follow up: at least 1 phone call and 2 certified letters before we can call a subject lost to follow up
- Sexually active patients who refuse to use medically accepted adequate birth control methods as described in the patient selection criteria during the course of the study and for a period of 120 days following discontinuation of study treatment.
- A female patient inadvertently becomes pregnant
- Request by regulatory agencies for termination of treatment of an individual patient or all patients under the protocol.
- Occurrence of a new malignancy.
    - Exceptions:
        - Patients with reported SAEs of non-melanoma skin cancer or in situ carcinoma may remain in the study at the discretion of the investigator and if discussed with medical monitor.
        - Patients with thin non-ulcerated primary melanoma
- The patient or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Administrative reasons

5.4.2 Part 2: After the First Recurrence (Cross-over or Re-challenge treatment)

Upon documented recurrence as per Section 7.1.1, patients may undergo surgery and radiotherapy if indicated. For systemic treatment see Sections below.

5.4.2.1 Crossover from placebo to pembrolizumab

Upon documented recurrence, adjuvant treatment will be unblinded as per Section 14.7.2.

Patients assigned to the placebo arm that meet all crossover criteria, (as per Section 4.2.1.1) will be offered to crossover to pembrolizumab and receive pembrolizumab 200 mg IV Q3W, if clinically indicated.

Patients will be separately consented for this part of the trial.

5.4.2.2 Administration of pembrolizumab after the first recurrence (Re-challenge)

Upon documented recurrence, patients assigned to pembrolizumab adjuvant arm who experience disease recurrence more than six months after completing one year of therapy may be re-treated with pembrolizumab 200 mg IV Q3W, if clinically indicated and if they fulfill criteria as per Sections 4.2 and 4.2.2.1.

Patients will be separately consented for this part of the trial.

5.4.2.3 Treatment duration for pembrolizumab

Treatment in Part 2 will be administered up to 1 year (local recurrence) or 2 years treatment period unless occurrence of a withdrawal criterion (see Section 5.4.2.4).

For patients with local recurrence, the treatment may stop at 1 year at the discretion of the investigator.

5.4.2.4 Withdrawal criteria for Part 2 treatment (Cross-over or Re-challenge treatment)

In part 2 (Cross-over or Re-challenge treatment) of the trial, a patient must be discontinued from treatment for this part of the trial (but may continue to be monitored in the trial) for any of the following reasons:

- Radiographic disease progression according to RECIST 1.1 (Appendix O)
- Completed up to 1 year (local recurrence) or 2 years of treatment with pembrolizumab (Section 5.4.2.3)
  - Note: duration of study medication is calculated from the date of first dose after first recurrence.
- AE or intercurrent illness that, in the opinion of the investigator, warrants the patient's withdrawal from study treatment
- Specific conditions described in the Management of Adverse Events (see Appendix G and Appendix H)
- Investigator's decision to withdraw the patient
- Noncompliance with study treatment or procedure requirements
  - Lost to follow up: at least 1 phone call and 2 certified letters before we can call a subject lost to follow up
- Sexually active patients who refuse to use medically accepted adequate birth control methods as described in the patient selection criteria during the course of the study and for a period of 120 days following discontinuation of study treatment.
- A female patient inadvertently becomes pregnant
- Request by regulatory agencies for termination of treatment of an individual patient or all patients under the protocol.

- Occurrence of a new malignancy.
  - Exceptions:
    - Patients with reported SAEs of non-melanoma skin cancer or in situ carcinoma may remain in the study at the discretion of the investigator and if discussed with medical monitor.
    - Patients with thin non-ulcerated primary melanoma
- The patient or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Administrative reasons

5.5 Management of Toxicity

For management of toxicity and supportive care guidelines please refer to Appendix G and Appendix H.

5.6 Concomitant medications

All treatments that the Investigator considers necessary for a patient'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 electronic case report form (eCRF) including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

All concomitant medications received within 30 days before the first dose of study drug through 30 days after the last dose of study drug should be recorded.

5.6.1 Prohibited medications, therapies and procedures

- Any anti-cancer treatment except those permitted in this trial (pembrolizumab and surgery)
  - After the first recurrence, radiotherapy is permitted before starting part 2.
- Any investigational agents other than the study drug
- Immunosuppressive agents (except for patients treated for irAE)
- Chronic systemic corticosteroids (except for patients which during the study developed endocrinopathies requiring stable doses of hormone replacement therapy such as hydrocortisone.)
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

6 Clinical evaluation, laboratory tests and follow-up

6.1 General considerations

The patient's written informed consent to undergo screening for the clinical trial must be given prior to the performance of any protocol laboratory/imaging tests that are not part of local routine guidelines. Therefore, if a patient had laboratory/imaging tests as part of local routine guidelines (standard of care) prior to signing informed consent, the procedures will be acceptable for screening purposes if they are within the window required by the protocol.

The Trial Flow Charts - Section 6.4 summarizes the trial procedures to be performed at each designated 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 patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature and thus local regulations may require that additional informed consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.1.1 Subject Identification Card

All patients 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 patient with a Subject Identification Card immediately after the patient provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about the trial medication in emergency situations where the investigator is not available.

6.2 Before treatment start

6.2.1 Within 8 weeks prior to randomization

A specific informed consent has been prepared to send the tumor sample for the level of PD-L1 expression and must be signed by the patient before the shipment of the tumor. This is mandatory.

FFPE tumor tissue will be collected from positive lymph nodes. Primary melanoma will also be collected if available. Samples are to be sent to central laboratory in order to check the PD-L1 status. For patients who consented to biobanking the tissue will thereafter be biobanked as per chapter 12.

6.2.2 Within 6 weeks prior to randomization

The patient's written informed consent to undergo screening for the clinical trial must be given prior to the performance of any protocol laboratory/imaging tests that are not part of local routine guidelines.

Upon confirmation of PD-L1 status and written informed consent, the following exams will be performed within a maximum of 6 weeks from ICF signature until the randomization) and results should be known before randomization:

- Eligibility criteria (see Section 3)
- Demographics, medical history, height
- Local testing for BRAF
- Physical examination (including pulse, blood pressure, temperature and weight)
- Assessment of adverse events
- ECOG performance status (see Appendix C)
- Urinalysis (specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed)
- Thyroid function: TSH; in case of elevated TSH to add free T3 and T4
- Cardiac function: 12-lead ECG
- Disease evaluation: the following imaging work up will be performed
  - Full Chest/Abdomen/Pelvis CT and/or MRI
  - Neck CT and/or MRI (for Head and Neck primaries)
  - Other CT and/or MRI (e.g. Brain, Deep Soft Tissue) only if clinically indicated
- Concomitant medications
- Health Related Quality of Life (HRQoL): within 6 weeks prior to randomization or at any point prior to treatment start
  - EORTC QLQ-C30 version 3 and EQ-5D-3L
- Translational research: for patient who consented
  - Two tubes of whole blood samples (5 mL each)
  - Serum and plasma samples (9 ml tube +/- 1mL each)

Please refer to Table 3 in Section 6.4.1.

6.2.3 Within 14 days (+/- 3 days) prior to treatment initiation

- Hematology: WBC, ANC, differential cell count, RBC, Hgb, Hct, Platelets
- Coagulation parameters: International Normalized Ratio (INR) or Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT)

- Serum chemistry: creatinine, urea or BUN, bilirubin, AST, ALT, alkaline phosphatase, LDH, total protein, K, Na, HCO3 (Japanese and German patients are excluded from HCO3 testing) and Ca, albumin, glucose, CRP

Please refer to Table 3 in Section 6.4.1.

Note: hematology and serum chemistry are to be repeated if performed more than 14 days prior to the first dose of study treatment.

6.2.4 Within 72 hours prior to treatment initiation

Women of child bearing potential must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment.

Note: the pregnancy test is to be repeated if performed more than 72 hours prior to the first dose of study treatment.

6.2.5 Within 24 hours prior to treatment initiation

- Pharmacokinetic (PK): one blood sample of at least 3.0 mL
- Anti-pembrolizumab antibody (ADA): one blood sample of 6 mL

6.3 During treatment

Pregnancy testing in women of child bearing potential . This pregnancy test is to be renewed/repeated during protocol treatment at the criteria of the investigator according to national regulations/institution guidelines.

Dosing delays

For laboratory assessments, physical exam, adverse events assessments, concomitant medication assessments, HRQoL and imaging work-up, if dose administration is delayed or held (e.g. patient on holiday, hospitalized, etc) but occurs later, the site should:

- Complete all protocol required laboratory tests, physical exam, adverse events assessments, concomitant medication assessments and HRQoL assessments within the required window prior to the new visit date of dose administration.
- Follow calendar days for imaging assessment and not adjust for cycle delays. The reference date for imaging scans should be day 1 cycle 1.

6.3.1 Part 1: Adjuvant Therapy

The visits for evaluations described below refer to study drug administrations. It's therefore expected that results of laboratory (hematology, serum chemistry, thyroid, urinalysis) and of imaging work ups are available prior to study drug administrations and within required timelines every 6 weeks (+/- 3 days) and every 12 weeks (+/- 7 days) depending on the type of evaluation.

Laboratory tests must be performed within maximum 3 days before study drug administration.

For imaging work ups and urinalysis it would be maximum 7 days.

6.3.1.1 Every 6 weeks (+/- 3 days)

The following exams will be performed every 6 weeks:

- Physical examination / ECOG performance status (see Section 6.2.2)
- Assessments of adverse events
- Hematology and serum chemistry (see Section 6.2.3). Results must be available prior to study drug administration and be drawn no longer than 3 days before study drug administration.
- Thyroid function (see Section 6.2.2). Results must be available prior to study drug administration and be drawn no longer than 3 days before study drug administration.
- Concomitant medications

Please refer to Table 3 in Section 6.4.1.

6.3.1.2 Every 12 weeks (+/- 7 days)

In addition to the above exams (see Section 6.3.1.1), the following exams will be performed every 12 weeks:

- Urinalysis (see Section 6.2.2). Results must be available prior to study drug administration.
- Imaging work up: results must be available before study drug administration.
  - Full chest/abdomen/pelvis CT and/or MRI
  - Neck CT and/or MRI (for head and neck primaries)
  - Other CT and/or MRI (e.g. brain, deep soft tissue) when clinically indicated, including and non-limited to:
    - Brain CT or MRI in case of headache or neurologic symptoms; chest CT in case of cough, dyspnea, thoracic pain; abdominal US or CT in case of abdominal pain, occlusive syndrome.

PET alone will not be used for the disease assessment. Superficial cutaneous lesions: the neoplastic nature must be confirmed by cytology/histology.

Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound and cytological/histological evidence must be obtained or these can be documented by CT scan in absence of pathology report

Cytology and/or histology are mandatory to confirm relapse in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions. Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases.

- Health Related Quality of Life (HRQoL) evaluations : EORTC QLQ-C30 version 3 and EQ-5D-3L

- Questionnaires are filled in every 12 weeks for the first two years and every 6 months up to 4th year (included). HRQoL data must be collected regardless of the patient's recurrence/progression status, unless patient withdraws from this part of the study.

In addition to above recommendations, if patients experience any adverse event or laboratory event during the treatment period, additional tests and/or visits will be performed as per recommendations in Appendix G and Appendix H.

Please refer to Table 3 in Section 6.4.1.

6.3.2 Translational research

Serial samples of plasma and serum (9 mL+/- 1 mL each) will be collected during the first year at week 4, week 13, 6 months and 12 months.

Note: It is acceptable to collect the baseline TR samples after randomization but before treatment start.

Please refer to Table 10 in Section 6.4.3.

6.3.3 Pharmacokinetic and anti-pembrolizumab antibody

Pre-dose trough PK (3.0 mL each) and ADA (6 mL each) samples will be collected at baseline week 1, week 4, week 10, week 22 and at 12 months (before the last infusion N°18).

All pre-dose blood samples should be drawn within 24 hours before infusion of pembrolizumab as described in the study Table 10 in Section 6.4.3.

6.3.4 End of adjuvant treatment (Part 1)

6.3.4.1 Discontinuation due to recurrence

Please refer to Table 4 (Section 6.4.1.1), Columns A and B for discontinuation due to recurrence

- Patients that did not complete the one year adjuvant treatment due to recurrence will be unblinded and will be offered to crossover if allowed per protocol qualifications in section 4.2. They should rapidly receive pembrolizumab after cross-over, and therefore the EOT visit should be done as soon as possible (site must not wait for 30 days).
- Patients who are not eligible for crossover/rechallenge will have the EOT visit at 30 days after last treatment dose (+/- 2 weeks).

For the EOT visit, the following exams will be performed:

- Pregnancy test in women of child bearing potential
- Physical examination / ECOG performance status
- Assessment of adverse events
  - If at the time of treatment discontinuation, the patient suffers from a severe (Grade 3 or 4) adverse event, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible. Any treatment related death occurring during and beyond this time frame must be reported to EORTC.

- Concomitant medications
- Hematology and serum chemistry see Section 6.2.3
- Urinalysis see Section 6.2.2
- Thyroid function see Section 6.2.2
- HRQoL see Section 6.3.4.3
- Imaging work up: in case of discontinuation due to recurrence, the recurrence scan date should be used as the reference date for scheduling future imaging scans. Baseline imaging scan prior to first dose in Part 2 should be within 4 weeks (+/- 7 days) of planned EOT visit. If the recurrence scan falls outside of this window, a new scan is required as baseline. Imaging includes CT with contrast or MRI of brain, chest, abdomen, pelvis and any specific body region based on the location of the primary melanoma (e.g. neck).Please refer to Table 4

6.3.4.2 Discontinuation in absence of recurrence

Please refer to Table 4 (Section 6.4.1.1), Columns C and D for discontinuation in absence of recurrence.

For patients who complete one year of adjuvant treatment in the absence of recurrence, the EOT visit should be performed at 30 days after the last treatment administration. **The following exams will be performed at 30 days +/- 2 weeks after the last treatment administration:**

- Pregnancy test in women of child bearing potential
- Physical examination / ECOG performance status
- Assessment of adverse events
  - If at the time of treatment discontinuation, the patient suffers from a severe (Grade 3 or 4) adverse event, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible. Any treatment related death occurring during and beyond this time frame must be reported to EORTC.
- Concomitant medications
- Hematology and serum chemistry see Section 6.2.3
- Urinalysis see Section 6.2.2
- Thyroid function see Section 6.2.2
- HRQoL see Section 6.3.4.3
- Imaging work up as per Section 6.3.1.2. In case of discontinuation of adjuvant treatment in the absence of disease recurrence, the date when imaging was performed for the EOT visit, should be used as the new reference date for scheduling future imaging scans.

Note: Patients discontinuing treatment in absence of recurrence, who had the last scan performed in the preceding 4 weeks (+/- 7 days) of planned EOT visit, may have the EOT scan omitted at the discretion of the investigator. In this case, for scheduling the next follow up visits, the date of last imaging work up will be used as reference. After EOT visit, all

assessments (imaging and all other exams, safety, etc.) will be performed on the same visit every 12 weeks.

Please refer to Table 4

6.3.4.2.1 Treatment discontinuation due to adverse event or ECI

A patient who discontinues treatment due to an AE/ECI and presents a recurrence after discontinuation may be eligible to be considered for Part 2, unless when there is a contraindication or the patient does not meet the eligibility criteria. Please contact the medical monitor on a per-case basis.

6.3.4.2.2 Treatment discontinuation due to patient's decision

A patient who discontinues treatment due to personal decision not described in the protocol, is considered permanently discontinued from treatment for the remainder of the study (Part 1 and Part 2).

6.3.4.3 HRQoL evaluation

Questionnaires (EORTC QLQ-C30 version 3 and EQ-5D-3L) will be filled in every 12 weeks for the first two years and every 6 months up to 4th year (included). HRQoL **data must be collected regardless of the patient's recurrence/progression status/treatment completion,** unless patient withdraws from this part of the study.

6.3.4.4 Translational research

Translational research samples of plasma and serum (9 mL+/- 1mL each) will be collected every 12 months (+/- 2 weeks) at years 2, 3, 4 and 5. After the 1st recurrence, collection of samples will continue only for patients who will cross-over or be re-challenged with pembrolizumab (Part 2). During Part 2, samples are collected regardless of the patient's recurrence/ progression status/treatment completion.

Please refer to Table 10

6.3.4.5 Pharmacokinetic and anti-pembrolizumab antibody

PK (3.0 mL each) and ADA (6 mL each) samples will be collected 30 days after discontinuation of study drug (or until another anti-cancer therapy is started). Every effort should be made to collect samples at these time-points.

Please refer to Table 10

6.3.5 Follow-up (after end of adjuvant treatment - Part 1)

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).

Participants in survival follow up should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

In addition, upon Sponsor request, participants may be contacted for survival status at any time points during the course of the study. For example, survival status may be requested prior to the eDMC safety review, efficacy interim analyses, and final analysis. All participants who are in the Survival Follow-Up Phase and not known to have died prior to the request for these additional survival status time points will be contacted at that time.

6.3.5.1 For patients who discontinued treatment due to recurrence but are not eligible for re-challenge or cross-over

Follow-up assessments for patients who discontinued due to recurrence but do not cross-over/re-challenge will be performed every 12 weeks (± 2 weeks) and the following information will be collected:

- HRQoL evaluation : EORTC QLQ-C30 version 3 and EQ-5D. Questionnaires are filled in every 12 weeks for the first 2 years and every 6 months up to 4th year (included). HRQoL data must be collected regardless of the patient's recurrence/progression status, unless patient withdraws from this part of the study.
- Record of further anti-cancer therapies on e-CRF and the outcomes
- Survival
- No imaging assessment is required for these patients during survival follow up

Please refer to Table 5.

6.3.5.2 For patients who discontinued due to patient's decision and are not eligible for re-challenge or cross-over

The patient will proceed to follow-up evaluations described in Table 5 for patients who discontinue but are not eligible for cross-over/re-challenge.

If patient does not withdraw consent, the following information will be collected:

- HRQoL evaluation : EORTC QLQ-C30 version 3 and EQ-5D. Questionnaires are filled in every 12 weeks for the first 2 years and every 6 months up to 4th year (included). HRQoL data must be collected regardless of the patient's recurrence/progression status, unless patient withdraws from this part of the study.
- Record of further anti-cancer therapies on e-CRF and the outcomes
- Survival
- No imaging assessment is required for these patients during survival follow up.

6.3.5.3 For patients who discontinued in absence of recurrence

The follow-up evaluations are described in Table 6 and will be performed every 12 weeks (± 2 weeks), unless otherwise noted below:

- Pregnancy test in women of child bearing potential

Note: pregnancy tests have to be repeated according to national regulations/institution guidelines.

- Physical examination / ECOG performance status

- Assessment of adverse events
- Concomitant medications
- Hematology and serum chemistry see Section 6.2.3
- Urinalysis see Section 6.2.2
- Thyroid function see Section 6.2.2
- Imaging work-up: follow up should still be provided for the study endpoints (RFS, DMFS, PRFS2 and OS). Imaging work up will be performed every 12 weeks for the first two years, every 6 months for the next 3 years (from year 3 to 5), and on the yearly basis thereafter.
- HRQoL evaluation : EORTC QLQ-C30 version 3 and EQ-5D. Questionnaires are filled in every 12 weeks for the first 2 years and every 6 months up to 4th year (included). HRQoL data must be collected regardless of the patient's recurrence/progression status, unless patient withdraws from this part of the study.

Upon first recurrence, the treatment arm should be unblinded per protocol procedures indicated in Section 14.7.2. If the patient qualifies for Part 2 please refer to Section 6.3.6.2. If patient does not proceed to Part 2 of the study, patient will be followed for survival and other therapies, but no further imaging assessments as per Section 6.3.5.1.

6.3.6 Part 2: cross-over or re-challenge treatment after the 1st recurrence

Upon documented recurrence, the patients will be considered for crossover to or re-challenge with pembrolizumab as per Sections 4.2.1.1 and 4.2.2.1

Patients have the option to consent for participation in the Part 2 after 1st recurrence.

6.3.6.1 Translational research

Patients who had previously signed consent for translational research at time of study registration in Part 1 of the study, will continue having research samples of plasma and serum (9mL+/- 1mL each) collected every 12 months (+/- 2 weeks) at years 2, 3, 4 and 5 regardless of the patient's recurrence/progression status/treatment completion.

Additionally, patients have the option to consent for Translational Research in Part 2 after recurrence and provide tumor material, if available.

6.3.6.2 Evaluations for patients receiving pembrolizumab

Please refer to Table 7 for evaluations during cross-over or re-challenge with pembrolizumab.

After signing the informed consent form, the following data will be collected every 12 weeks (± 2 weeks) until disease progression/ second recurrence or up to the end two year treatment period:

- Women of child bearing potential must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment in Part 2 of the study. This

pregnancy test is to be renewed/repeated during protocol treatment at the criteria of the investigator according to national regulations/institution guidelines.

- Physical examination / ECOG performance status
- Adverse events
- Concomitant medication
- Hematology and serum chemistry see Section 6.2.3
- Urinalysis see Section 6.2.2
- Thyroid function see Section 6.2.2
- HRQoL evaluation see Section 6.3.4.3
- Imaging assessments

  Baseline imaging scan prior to first dose in Part 2 should be within 4 weeks (+/- 7 days) of planned EOT visit. If the recurrence scan falls outside of this window, a new scan is required as baseline. Baseline imaging includes CT with contrast or MRI of brain, chest, abdomen, pelvis and any specific body region based on the location of the primary melanoma (e.g. neck).

  Imaging work up during Part 2 of the study will be at 12 weeks after the first dose, then every 12 weeks until disease progression/ second recurrence or completion of treatment (up to 1 year (local recurrence) or 2 years treatment period unless occurrence of a withdrawal criterion).Imaging during Part 2 treatment includes full chest/abdomen/pelvis CT and/or MRI; Neck CT and/or MRI (for head and neck primaries); other CT and/or MRI (e.g. Brain, Deep Soft Tissue) when clinically indicated, including and not limited to: Brain CT or MRI in case of headache or neurologic symptoms; chest CT in case of cough, dyspnea, thoracic pain; abdominal US or CT in case of abdominal pain, occlusive syndrome

Upon disease progression or second recurrence or after the completion of treatment period, please refer to Section 6.3.8.1

6.3.7 End of treatment (Part 2)

6.3.7.1 Discontinuation due to progression or 2nd recurrence

The EOT visit should be performed at 30 days +/- 2 weeks after the last treatment administration and the following exams will be performed:

- Pregnancy test in women of child bearing potential
- Physical examination / ECOG performance status
- Assessment of adverse events
  - If at the time of treatment discontinuation, the patient suffers from a severe (Grade 3 or 4) adverse event, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible. Any treatment related death occurring during and beyond this time frame must be reported to EORTC.

- Concomitant medications
- Hematology and serum chemistry see Section 6.2.3
- Urinalysis see Section 6.2.2
- Thyroid function see Section 6.2.2
- HRQoL to assess if needed as per Section 6.3.4.3

Please refer to Table 8.

6.3.7.2 Discontinuation in absence of recurrence

The following exams will be performed at 30 days +/- 2 weeks after the last treatment administration:

- Pregnancy test in women of child bearing potential
- Physical examination / ECOG performance status
- Assessment of adverse events
  - If at the time of treatment discontinuation, the patient suffers from a severe (Grade 3 or 4) adverse event, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible. Any treatment related death occurring during and beyond this time frame must be reported to EORTC.
- Concomitant medications
- Hematology and serum chemistry see Section 6.2.3
- Urinalysis see Section 6.2.2
- Thyroid function see Section 6.2.2
- HRQoL to assess if needed as per Section 6.3.4.3
- Imaging work up:

Please refer to Table 8.

6.3.8 Follow-up (after end of pembrolizumab in Part 2)

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).

Participants in survival follow up should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

In addition, upon Sponsor request, participants may be contacted for survival status at any time points during the course of the study. For example, survival status may be requested prior to the eDMC safety review, efficacy interim analyses, and final analysis. All participants who are in the Survival Follow-Up Phase and not known to have died prior to the request for these additional survival status time points will be contacted at that time.

6.3.8.1 For patients who discontinued Part 2 due to progression or recurrence or completion of treatment

Follow-up assessments for patients who discontinued Part 2 will be performed every 12 weeks (± 2 weeks) and the following information will be collected:

- HRQoL to assess if needed as per Section 6.3.4.3
- Record of further anti-cancer therapies on e-CRF and the outcomes
- No imaging assessment is required for these patients during survival follow up
- Survival

Please refer to Table 9.

6.3.8.2 Treatment discontinuation due to adverse event or ECI

A patient who discontinues treatment due to an AE/ECI will be followed up for safety and overall survival.

6.3.8.3 Treatment discontinuation due to patient's decision

A patient who discontinues treatment due to personal decision not described in the protocol, is considered permanently discontinued from treatment for the remainder of the study

6.4 Summary Tables

6.4.1 Part 1: Evaluations during adjuvant treatment (Part 1)

	Prior to randomization		**Prior to treatment initiation**		**Treatment period**		**At end of adjuvant treatment**
	Within 8 weeks	Within 6 weeks	Within 14 days	Within 72 hours	Q 6 wks	Q 12 wks	Discontinuation due to recurrence or in absence of recurrence
Window to perform investigations					**+/- 3 days**	**+/- 7 days**	
Informed consents	♦	♦					**Refer to Table 4**
Pregnancy test[1]				♦	#	#	
Tumor sample for PD-L1 test[2]	♦						
Eligibility		♦					
BRAF status		♦					
Medical history, height demographics		♦					
Physical examination (weight, pulse, BP, T, ECOG PS)[3]		♦			♦		
Adverse events		♦			♦		
Concomitant medications		♦			♦		
Hematology [4]			♦		♦		
Serum or plasma chemistry [4]			♦		♦		
Coagulation parameters[4]			♦				
Urine analysis[5]		♦				♦	
Thyroid function[6]		♦			♦		
12-lead ECG		♦					
HRQoL[7]		♦				♦	
Imaging work up[8]		♦[8]				♦[9]	

	Prior to randomization		Prior to treatment initiation		Treatment period		At end of adjuvant treatment
	Within 8 weeks	Within 6 weeks	Within 14 days	Within 72 hours	Q 6 wks	Q 12 wks	Discontinuation due to recurrence or in absence of recurrence
Window to perform investigations					**+/- 3 days**	**+/- 7 days**	
Survival [10]	Refer to Table 7 for cross-over or rechallenge Refer to Table 5 for patients that will not cross-over or be re-challenged Refer to Table 6 for patients who discontinued in absence of recurrence						
Anticancer therapies	Refer to Table 7 for cross-over or rechallenge Refer to Table 5 for patients that will not cross-over or be re-challenged Refer to Table 6 for patients who discontinued in absence of recurrence						

♦ in all cases # as per national regulations/institutions guidelines

1. Women of child bearing potential must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment. Note: the pregnancy test is to be repeated if performed more than 72 hours prior to the first dose of study treatment.

2. PD-L1 testing: tumor material will be collected from positive lymph nodes (LN) embedded in paraffin. If the resection samples from LNs are not adequate for PD-L1 testing, the primary melanoma must be collected. Patients whose samples are inadequate for PD-L1 determination will not be randomized. In addition to the resection samples from LNs, the primary melanoma may also be collected if available to evaluate the PD-L1 expression

3. Physical examination includes ECOG performance status, blood pressure, weight, pulse rate, temperature

4. Complete blood count: WBC, ANC, differential cell count, RBC, Hgb, Hct, Platelets and serum or plasma chemistry: creatinine, urea or BUN , bilirubin, AST, ALT, alkaline phosphatase, LDH, total protein, K, Na, HCO3 (Japanese and German patients are excluded from HCO3 testing) and Ca, albumin, glucose, CRP. Coagulation parameters at baseline: INR or PT and aPTT.
Note: hematology and serum chemistry are to be repeated if performed more than 14 days prior to the first dose of study treatment.

5.Urine analysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed

6.Thyroid function: TSH; in case of elevated TSH to add free T3 and T4

7.HRQoL questionnaires (EORTC QLQ-C30 version 3 and EQ-5D-3L) are filled in at baseline within 6 weeks prior to randomization or at any point prior to treatment start, then every 12 weeks for the first 2 years and every 6 months up to the 4th year (included). HRQoL data must be collected regardless of the patient's recurrence/progression status , unless patient withdraws from this part of the study.

8. Imaging work up: Full chest/abdomen/pelvis CT and/or MRI; Neck CT and/or MRI (for head and neck primaries); other CT and/or MRI (e.g. Brain, Deep Soft Tissue) when clinically indicated, including and not limited to: Brain CT or MRI in case of headache or neurologic symptoms; chest CT in case of cough, dyspnea, thoracic pain; abdominal US or CT in case of abdominal pain, occlusive syndrome

9. During adjuvant treatment imaging will be performed at baseline, then every 12 weeks after first dose until recurrence or end of adjuvant treatment phase.

10. Upon Sponsor request, participants may be contacted for survival status at any time points during the course of the study.

Table 3: Evaluations during adjuvant therapy

6.4.1.1 Overview EOT for adjuvant treatment (Part 1)

	At end of adjuvant treatment			
	Discontinuation due to recurrence		Discontinuation in absence of recurrence[2]	
	A	B	C	D
	Discontinued before completion of adjuvant treatment and **will not** proceed to Part 2 (visit 30 days after last dose or before new therapy, whichever is sooner)	Discontinued before completion of adjuvant treatment and **will proceed** to Part 2 (visit as soon as possible)	If adjuvant therapy completed (visit 30 days after last dose	If discontinued before completion of adjuvant therapy (visit 30 days after last dose)
Window to perform investigations	**+/- 2 weeks**	**as soon as possible**	**+/- 2 weeks**	**+/- 2 weeks**
Pregnancy test	♦	♦	♦	♦
Physical examination [1] (weight, pulse, BP, T, ECOG PS)	♦	♦	♦	♦
Adverse events	♦	♦	♦	♦
Concomitant medications	♦	♦	♦	♦
Hematology [2]	♦	♦	♦	♦
Serum or plasma chemistry [2]	♦	♦	♦	♦
Urine analysis[3]	♦	♦	♦	♦
Thyroid function[4]	♦	♦	♦	♦
HRQoL[5]	♦	♦	♦	♦
Imaging work up	♦[6]	♦[7]	♦[8]	♦[8]

	At end of adjuvant treatment			
	Discontinuation due to recurrence		Discontinuation in absence of recurrence[2]	
	A	B	C	D
	Discontinued before completion of adjuvant treatment and **will not** proceed to Part 2 (visit 30 days after last dose or before new therapy, whichever is sooner)	Discontinued before completion of adjuvant treatment and **will proceed** to Part 2 (visit as soon as possible)	If adjuvant therapy completed (visit 30 days after last dose	If discontinued before completion of adjuvant therapy (visit 30 days after last dose)
Window to perform investigations	**+/- 2 weeks**	**as soon as possible**	**+/- 2 weeks**	**+/- 2 weeks**

♦ in all cases

1. Physical examination includes ECOG performance status, blood pressure, weight, pulse rate, temperature

2. Complete blood count: WBC, ANC, differential cell count, RBC, Hgb, Hct, Platelets and serum or plasma chemistry: creatinine, urea or BUN, bilirubin, AST, ALT, alkaline phosphatase, LDH, total protein, K, Na, HCO3 (Japanese and German patients are excluded from HCO3 testing)and Ca, albumin, glucose, CRP

3. Urine analysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed

4. Thyroid function: TSH; in case of elevated TSH to add free T3 and T4

5. HRQoL questionnaires (EORTC QLQ-C30 version 3 and EQ-5D-3L) that started during adjuvant treatment are filled in every 12 weeks for the first 2 years and every 6 months up to 4th year (included).

Note: HRQoL data must be collected regardless of the patient's recurrence/progression status/treatment completion, unless patient withdrawal from this part of the study, unless patient withdraws from this part of the study.

6. Imaging scan for EOT visit is considered the scan taken at recurrence. Patients who discontinue due to recurrence before completion of adjuvant treatment and will not proceed to Part 2 will not require further imaging scans, and will continue to survival follow up per section 6.3.5.1

7. Patients who did not complete the one year adjuvant treatment due to recurrence will be unblinded and will be offered to crossover if allowed per protocol qualifications in section 4.2. They should rapidly receive pembrolizumab after cross-over. And therefore the EOT visit should be done as soon as possible (site must not wait for 30 days) as per section 6.3.4.1.

Note: the recurrence scan date should be used as the reference date for scheduling future imaging scans.Baseline imaging scan prior to first dose in Part 2 should be within 4 weeks (+/- 7 days) of planned EOT visit. If the recurrence scan falls outside of this window, a new scan is required as baseline. Imaging includes CT with contrast or MRI of brain, chest, abdomen, pelvis and any specific body region based on the location of the primary melanoma (e.g. neck).

8. After completion of adjuvant treatment in absence of recurrence, follow-up imaging will be performed every 12 weeks for the first two years, every 6 months for the next 3 years (from year 3 to 5), and then on a yearly basis thereafter.
Patients who discontinue adjuvant treatment for other reason than recurrence should follow procedures per sections 6.3.5.2. or 6.3.5.3

Table 4: Evaluations for EOT

6.4.1.2 Follow-up evaluation Part 1: for patients who discontinue due to recurrence but do not cross-over/re-challenge or due to patient's decision

Follow-up assessments	**Every 12 weeks (+/- 2 wks after EOT) after discontinuation or recurrence**
HRQoL [1]	♦
Survival [2]	♦
Record anticancer therapies and outcomes[2]	♦
Imaging work up[3]	♦

♦ in all cases

1. HRQoL questionnaires (EORTC QLQ-C30 version 3 and EQ-5D-3L) are filled in every 12 weeks for the first 2 years and every 6 months up to 4th year (included). HRQoL data must be collected regardless of the patient's recurrence/progression status/treatment completion, unless patient withdraws from this part of the study.

2. Upon disease progression/second recurrence during Part 1 or after Part 1 treatment discontinuation, whichever is first. Upon Sponsor request, participants may be contacted for survival status at any time points during the course of the study.

Note: Survival follow up and record of anticancer therapies and outcomes will be conducted via phone calls once there are no further HRQoL questionnaires scheduled for completion.2. After first recurrence during Part 1. Upon Sponsor request, participants may be contacted for survival status at any time points during the course of the study

3. Patients without distant metastasis detected, will continue imaging assessments every 12 weeks for the first two years, every 6 months for the next 3 years (from year 3 to 5), and on a yearly basis thereafter until detection of distant metastasis or patient withdrawal of consent.

Table 5: Follow up evaluations for patients who discontinue Part 1due recurrence (but no cross-over or rechallenge) or patient's decision

6.4.1.3 Follow-up evaluation Part 1: for patients who discontinued in absence of recurrence

	Every 12 weeks (+/- 2 wks) after EOT
Pregnancy test	♦
Physical examination/ECOG PS	♦
Adverse events	♦
Concomitant medications	♦
Hematology and serum chemistry	♦
Urinalysis	♦
Thyroid function	♦
HRQoL[1]	♦
Imaging work up[2]	♦

♦ in all cases

1. HRQoL questionnaires (EORTC QLQ-C30 version 3 and EQ-5D-3L) that started during adjuvant treatment are filled in every 12 weeks for the first 2 years and every 6 months up to 4th year (included).

Note: HRQoL data must be collected regardless of the patient's recurrence/progression status/treatment completion, unless patient withdrawal from this part of the study.

2. Imaging work up will be performed every 12 weeks for the first two years, every 6 months for the next 3 years (from year 3 to 5), and on the yearly basis thereafter.

NOTE: Upon first recurrence, the treatment arm should be unblinded per protocol procedures indicated in Section 14.7.2. If the patient qualifies for Part 2 of the study, the follow-up will be as per Section 6.3.6.2. Patients who do not proceed to Part 2 of the study will be followed for survival and other therapies, but no further imaging assessments as per Section 6.3.5.1

Table 6: Follow-up evaluations for patients discontinued in absence of recurrence

6.4.2 Part 2: Cross-over or rechallenge after the 1st recurrence

6.4.2.1 Evaluations during cross-over or re-challenge with pembrolizumab

	Evaluation every 12 weeks (± 2 weeks) up to 1 year (local recurrence) or 2 years treatment period unless occurrence of a withdrawal criterion	Imaging evaluation every 12 weeks until disease progression
Informed consent	♦	
Pregnancy test [1]	#	
Physical examination (weight, pulse, BP, T) ECOG PS [2]	♦	
Adverse events	♦	
Concomitant medications	♦	
Hematology [3]	♦	
Serum or plasma chemistry [3]	♦	
Urine analysis[4]	♦	
Thyroid function [5]	♦	
HRQoL [6]	♦	
Imaging work up [7]		♦

♦ in all cases # as per national regulations/institutions guidelines

1. Women of child bearing potential must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment in Part 2 of the study.

2. Physical examination includes ECOG performance status, blood pressure, weight, pulse rate, temperature

3. Complete blood count: WBC, ANC, differential cell count, RBC, Hgb, Hct, Platelets and serum or plasma chemistry: creatinine, urea or BUN, bilirubin, AST, ALT, alkaline phosphatase, LDH, total protein, K, Na, HCO3 (Japan and German patients are excluded from HCO3 testing) and Ca, albumin, glucose, CRP

4. Urine analysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed

5. Thyroid function: TSH; in case of elevated TSH to add free T3 and T4

6. HRQoL questionnaires (EORTC QLQ-C30 version 3 and EQ-5D) are filled in every 12 weeks for the first 2 years and every 6 months up to 4th year (included). HRQoL data must be collected regardless of the patient's recurrence/progression statuts, unless patient withdraws from this part of the study.

7. Baseline imaging scan prior to first dose in Part 2 should be within 4 weeks (+/- 7 days) of planned EOT visit. If the recurrence scan falls outside of this window, a new scan is required as baseline. Baseline imaging includes CT with contrast or MRI of brain, chest, abdomen, pelvis and any specific body region based on the location of the primary melanoma (e.g. neck). Imaging work up during Part 2 of the study will be at 12 weeks after the first dose, then every 12 weeks until disease progression/ second recurrence/ or completion of treatment (up to 1 year (local recurrence) or 2 years treatment period unless occurrence of a withdrawal criterion). Imaging during Part 2 treatment includes full chest/abdomen/pelvis CT and/or MRI; Neck CT and/or MRI (for head and neck primaries); other CT and/or MRI (e.g. Brain, Deep Soft Tissue) when clinically indicated, including and not limited to: Brain CT or MRI in case of headache or neurologic symptoms; chest CT in case of cough, dyspnea, thoracic pain; abdominal US or CT in case of abdominal pain, occlusive syndrome

Table 7: Evaluations during cross-over or re-challenge with pembrolizumab

6.4.2.2 Overview EOT (Part 2)

	EOT visit	
	Discontinuation due to progression or 2nd recurrence	Discontinuation in absence of progression or 2nd recurrence
Window to perform investigations	**30 days +/- 2 weeks**	**30 days +/- 2 weeks**
Pregnancy test	♦	♦
Physical examination [1] (weight, pulse, BP, T, ECOG PS)	♦	♦
Adverse events	♦	♦
Concomitant medications	♦	♦
Hematology [2]	♦	♦
Serum or plasma chemistry [2]	♦	♦
Urine analysis[3]	♦	♦
Thyroid function[4]	♦	♦
HRQoL[5]	♦	♦
Imaging work up		♦

1. Physical examination includes ECOG performance status, blood pressure, weight, pulse rate, temperature
2. Complete blood count: WBC, ANC, differential cell count, RBC, Hgb, Hct, Platelets and serum or plasma chemistry: creatinine, urea or BUN, bilirubin, AST, ALT, alkaline phosphatase, LDH, total protein, K, Na, HCO3 (Japan and German patients are excluded from HCO3 testing) and Ca, albumin, glucose, CRP
3. Urine analysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed
4. Thyroid function: TSH; in case of elevated TSH to add free T3 and T4
5. HRQoL questionnaires (EORTC QLQ-C30 version 3 and EQ-5D) : to assess if needed as Section 6.3.4.3

Table 8. Evaluation for EOT visit

6.4.2.3 Follow-up evaluation for patients who discontinue Part 2

Follow-up assessments	**Every 12 weeks (+/- 2 wks after EOT)**
HRQoL [1]	♦
Survival [2]	♦
Record anticancer therapies and outcomes[2]	♦
Imaging work up[3]	♦

♦ in all cases

1. HRQoL questionnaires (EORTC QLQ-C30 version 3 and EQ-5D-3L): to assess if needed as Section 6.3.4.3

2. Upon disease progression/second recurrence during Part 2 or after Part 2 treatment discontinuation, whichever is first. Upon Sponsor request, participants may be contacted for survival status at any time points during the course of the study

Note: Survival follow up and record of anticancer therapies and outcomes will be conducted via phone calls once there are no further HRQoL questionnaires scheduled for completion.

3. Patients without distant metastasis detected, will continue imaging assessments every 12 weeks (from last scan in Part 2) for the first two years, every 6 months for the next 3 years (from year 3 to 5), and on a yearly basis thereafter until detection of a distant metastasis (if not detected in Part 1) or patient withdrawal of consent.

Table 9: Follow up evaluations for patients who discontinue Part 2

6.4.3 Blood, serum and tumor samples

Samples	Prior to random		Within 24 hrs prior to treat. start	Treatment Period						After end of adjuvant treatment (EOT)*	
	Within 8 wks	Within 6 wks		Wk4	Wk 10	Wk 13	Wk 22	6 mo	12 mo	30 days after last dose	Years 2-3-4-5 Q12 months
TR FFPE	♦										
TR whole blood samples[1]		♦									
TR Serum and Plasma samples[2]		♦		♦		♦		♦	♦		♦
PK samples[3]			♦	♦	♦		♦		♦	♦	
ADA samples[3]			♦	♦	♦		♦		♦	♦	

♦ in all cases

* Samples are collected regardless of the patient's recurrence/ progression status/treatment completion and for patients receiving pembrolizumab.

1. Two tubes of 5 mL each. It is acceptable to collect the TR samples after randomization but before treatment start.

2. Serial samples of serum and plasma (9 ml +/- 1mL each) will be collected during the first year: at baseline before treatment initiation (timepoint 0), week 4, week 13, then at 6 and 12 months. For the next years (2-3-4-5), every 12 months. It is acceptable to collect the TR samples after randomization but before treatment start.

3. All pre-dose blood samples should be drawn within 24 hours before infusion of pembrolizumab: prior to treatment start, week 4, week 10 , week 22 and at 12 months (before last infusion N°18).
PK (3 mL each) and ADA (6 mL each) samples will also be collected 30 days after discontinuation of study drug (or until starts new anti-cancer therapy).

As PK and ADA samples are collected within 24 hours before infusion: if treatment has to be postponed the collection of PK and ADA samples has to be adjusted accordingly.

Table 10: Timeschedule for blood, serum and tumor samples collection

7 Criteria of evaluation

7.1 Evaluation of efficacy

7.1.1 Recurrence

7.1.1.1 Definition

Recurrence is defined as appearance of one or more new melanoma lesions: local, regional or distant (Ref. 59).

- **Local cutaneous recurrence**:
  - It is generally accepted that local recurrences occur within 2 cm of the tumor bed. Its neoplastic nature must be confirmed either by histology/cytology
    - Local recurrence after inadequate excision of the primary lesion occurs usually at the periphery of the previous surgical bed. In such instances, the risk of distant metastases and death may be similar to that of primary lesions with the same thickness, ulceration, and nodal status.
    - Local recurrence after adequate surgical excision of the primary melanoma is associated with aggressive tumor biologic features and is frequently a harbinger of metastases.
- **Regional lymphatic and nodal recurrences**: The neoplastic nature of the regional recurrences should be attempted and confirmed by histology/cytology.
  - In Transit Metastases:
    - The American Joint Committee on Cancer (AJCC) defines in transit metastases as any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but are not beyond the regional nodal basin. In transit metastases occur in 10% to 15% of patients with stage III disease. When present, in transit metastases are usually multiple, evolve over time and are often the harbinger of subsequent systemic disease.
  - Regional Nodal Recurrences: Regional nodal failure in a previously dissected basin is usually found at the periphery of the prior surgical procedure.
- **Distant metastases**:
  - Patterns of Metastases: Melanoma is well known for its ability to metastasize to virtually any organ or tissue. The most common initial sites of distant metastases are the non–visceral as the skin, subcutaneous tissue, and lymph nodes, which are recurrence sites for 42% to 59% of patients in various studies. Visceral locations are the lung, brain, liver, gastrointestinal tract, and bone which are the initial sites of relapse in approximately 25% of all melanoma patients who experienced recurrence.
  - Distant metastases may be measurable or non-measurable lesions:
    - Measurable disease - the presence of at least one measurable lesion.

- Single measurable lesions (visceral or nodal) should measure ≥ 10 mm in two dimensions. If the measurable disease is restricted to a solitary lesion (visceral or nodal), its neoplastic nature must be confirmed either by cytology/histology either by lesion progression certified on the next CT/MRI examination.
- Multiple measurable lesions - lesions that can be accurately measured with spiral CT scan must be ≥ 10 mm in at least one dimension.

♦ Non-measurable lesions - all other lesions, including small lesions (< 10 mm with spiral CT scan) and other non-measurable lesions. Other non measurable lesions include but are not limited to: bone lesions; leptomeningeal disease; ascites; pleural / pericardial effusion; inflammatory breast disease; lymphangitis cutis / pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions.

Note:

♦ Cutaneous relapses occurring beyond the periphery of the previous surgical bed (i.e. over 2 cm) are considered distant metastases.

♦ Node relapses occurred beyond the anatomical compartment of the dissected basins are considered distant metastases.

♦ Node relapses in nodal basins situated in a different anatomical compartment or beyond the previously dissected basin or in two nodal basins (even if contiguous; i.e. 2 pelvic nodal basins, 2 mediastinal nodal basins) are considered distant metastases.

7.1.1.2 Methods of measurements

♦ CT and MRI are mandatory to establish recurrence. Conventional CT with i.v. contrast and MRI gadolinium should be performed with contiguous cuts of 10 mm or less slice thickness. Spiral CT should be performed using a 3 or 5 mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen and pelvis while head & neck tumors and those of the extremities usually require specific protocols. In each institute the same technique for CT/MRI should be used to characterize each new lesion.

♦ PET alone will not be considered for the disease assessment. Complementary CT/MRI or biopsy must be performed in such cases.

♦ Cytology and/or histology are mandatory to confirm recurrence in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions. Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases.

♦ Clinically detected new lesions:

- ♦ Superficial cutaneous lesions: the neoplastic nature must be confirmed by cytology/histology.
- ♦ Deep subcutaneous lesions and lymphnode lesions should be documented by ultrasound and histological/cytological evidence should be attempted. In absence of

pathology report, lesion progression (recurrence) will be documented with a CT scan/MRI.

7.1.1.3 Date of recurrence

The first date when recurrence was observed is taken into account regardless the method of assessment. Therefore recurrence will be declared for any lesion when:

- Only imaging was performed and progression confirmed
- Only pathology was done and malignancy confirmed (in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions)
- Both pathology and imaging were done and progression/malignancy confirmed. In this case, whatever examination came first, its date is considered to be the date of recurrence.

7.1.2 Progression During Part 2 (Cross-over/Re-challenge)

Refer to Section 5.4.2.4 for reasons to discontinue treatment during the cross-over/re-challenge treatment part.

Treatment after Initial Radiologic Progression During Cross-over/Re-challenge Portion of Trial

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.

If radiologic imaging shows progression of disease during cross-over/re-challenge treatment although patient appears to have a clinical benefit according to investigator's judgment, tumor assessment may be repeated by the site ≥4 weeks later in order to confirm progression of disease 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 progression of disease, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, patients will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

The decision to continue study treatment after the first evidence of disease progression during cross-over/re-challenge treatment is at the Investigator's discretion based on the clinical status of the patient.

Patients may receive study treatment while waiting for confirmation of progression of disease if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease

- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Discontinuation of Study Therapy after Complete Response

Discontinuation of cross-over/re-challenge treatment may be considered for patients who have attained a confirmed complete response that have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial complete response was declared.

7.1.3 Time to event endpoints

7.1.3.1 Recurrence-free survival

Recurrence-free survival (RFS) is defined as the time between the date of randomization and the date of first recurrence (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. For patients who remain alive and whose disease has not recurred, RFS will be censored on the date of last visit/contact with disease assessments. RFS will be based on the disease assessment or date of death provided by the local investigator.

All imaging (radiologic) from a sample of patients will be reviewed in a blinded fashion by an Independent Review Committee to assess recurrence. The IRC review is defined in a separate IRC charter.

7.1.3.2 Distant metastasis-free survival

Distant metastasis-free survival (DMFS) is defined as the time between the date of randomization and the date of 1st distant metastasis or date of death (whatever the cause), whichever occurs first. For patients who remain alive and distant metastasis-free, DMFS will be censored on the date of last visit/contact with disease assessments. DMFS will be based on the 1st date of distant metastasis assessment or date of death provided by the local investigator.

7.1.3.3 Duration of overall survival

Overall survival (OS) is defined as the time from the date of randomization to the date of death, whatever the cause. The follow-up of patients still alive will be censored at the moment of last visit/contact.

7.1.3.4 Duration of progression/recurrence-free survival 2

Progression/recurrence-free survival 2 (PRFS2) is defined as the time between the date of randomization and the earliest of the following:

- date of 1st disease progression per RECIST 1.1 (Appendix O) beyond the initial unresectable disease recurrence (e.g. unresectable distant metastases);
- date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (e.g. local regional recurrences or resectable distant metastases);
- death.

For patients who remain alive and whose disease has not recurred, or disease has recurred but subsequent disease progression or recurrence has not occurred, PRFS2 will be censored on the date of last visit/contact with disease assessments or date of last follow up.

7.2 Evaluation of safety

7.2.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

All adverse events must be followed until resolution or stabilization.

7.2.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page www.eortc.org\investigators-area\ctc.

Hematological toxicity will be assessed on the basis of regular blood tests. The nadir count will be computed at each study medication administration and graded according to the CTCAE version 4.0.

Non hematological acute side effects will be assessed and reported separately for each study medication administration, and graded according to the CTCAE version 4.0.

Planned safety analysis and tabulations are described in the statistics Section 8.

7.2.3 Serious adverse events and Events of Clinical Interest

Serious adverse events are defined by the Good Clinical Practice Guideline.

Serious adverse events should be immediately reported according to the procedure detailed in this PROTOCOL (see chapter on Reporting Serious Adverse Events).

For guidance regarding Events of Clinical Interest (ECI) for pembrolizumab please refer to Appendix H.

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.2.5 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

8 Statistical considerations

8.1 Statistical design

This is a double-blind randomized phase III trial.

8.1.1 Sample size

The primary objective of this study is to determine whether post-operative adjuvant therapy with Pembrolizumab improves recurrence-free survival (RFS) (definition: Section 7.1.3.1) as compared to placebo in patients with complete resection of stage IIIA (>1 mm metastasis), IIIB and IIIC (no past or current in-transit metastases or satellitosis) melanoma (AJCC 2010). Also, whether in PD-L1-positive expression subgroup, Pembrolizumab improves RFS. Secondary efficacy endpoints (DMFS and OS) will evaluate whether an immediate administration of Pembrolizumab improves the outcome as compared to those who initially received placebo, even if cross-over from placebo to Pembrolizumab after a 1st recurrence is performed. As for RFS endpoint, the impact of Pembrolizumab on these 2 secondary efficacy endpoints will be evaluated in the subgroup of PD-L1-positive expression subgroup as well.

In the observation group of the EORTC 18991 study, stage IIIb/IIIc patients had a median RFS of 1.1 yr, the 1-yr RFS rate was 54% and the 3-yr RFS rate was 33%. On the other hand, stage IIIA patients had a 1-yr RFS of 90% and 3-yr RFS of 65%.

In this new trial, one expects that patient population will be represented by a mixture of Stage IIIA (> 1 mm) (20%) and stage IIIb/IIIc (80%). In the EORTC 18071 study, the stage distribution was: Stage IIIA (> 1 mm) (20%), stage IIIb (45%) and stage IIIc (35%). In such a mixed population, based on the results of the 18071 study (Q12014), one may expect in the control group (placebo) a RFS hazard rate of 0.045 per month during the first year (so a cumulative hazard rate of 0.54 per year), a RFS hazard rate of 0.02 per month years 1 to 3 (so a cumulative hazard rate of 0.25 per year), and 0.005 per month thereafter (so a cumulative hazard rate of 0.06 per year). Therefore, in the placebo group the expected 1-yr RFS rate is 58.3% and the 3-yr RFS rate is 35.3%. Based on piece-wise exponential assumption, the expected median RFS in the placebo arm is 1.64 years (19.7 months). Such estimates are quite reasonable, as in the 18071 trial, the 1-yr and 3-yr RFS rates based on the local investigator was 57.4% and 35.9% respectively, and the median estimation was 17.5 months.

The study is powered for the primary endpoint, RFS. Assuming RFS hazard rates for placebo of 0.54 pre- 1 year and 0.25 post-1 year from randomization, a total of 409 events (local/regional/distant metastasis/death) for RFS are needed to provide 95% power to detect an Pembrolizumab:placebo hazard ratio (HR) of 0.70 (1-sided logrank test, alpha=2.5%) or an increase of the median RFS from 1.64 to 2.87 years (median ratio=1.75). This corresponds also to an increase of 10.2% (from 58.3% to 68.5%) in the 1-year RFS rate (see Table 11). The power could also be 92% according to the multiplicity strategy which allocates alpha=1.4% to RFS (discussed below).

	Endpoint: RFS **Hazard ratio (HR) = 0.70 , 1-sided alpha=1.4%, power=92%** **Hazard ratio (HR) = 0.70 , 1-sided alpha=2.5%, power=95%**							
	Expected RFS rate at			**Hazard rate (lambda) per year**				**Total nb. of pts: 900**
	1-yr	3-yr	7-yr	<=1 yr	1-<3 yr	3+ yrs	Total nb. of RFS Events	100 pts/first 6 months 200 pts/month 7-12 600 pts/2nd year
Placebo	58.3%	35.3%	27.8%	0.54	0.25	0.06	409	Accrual: 2 yrs ± additional follow-up: 1 year ± total follow-up: 3 years
Pembrolizumab	68.5%	48.3%	40.8%	0.38	0.175	0.0042		
Difference/HR	10.2%	13.0%	13.0%	0.7	0.7	0.7		

Table 11: Estimations of RFS events

In this study it is planned to randomize a total of approximately 900 eligible patients (approximately 450 patients per arm)

Up to 2.5% additional patients may be enrolled in order to compensate:

- Ineligible patients
- Early consent withdrawal

In addition, if by the time the targeted enrollment is completed there are patients in consenting process, they will be authorized to be randomized in the study.

Assuming that the entry rate will be, on average, 100 patients/first 6 months 200 patients/month 7-12, and 600 patients/2nd year, the total accrual period will be approximately 2 years. If one assumes that the hazard of patient drop-out for RFS evaluation

will be 0.015 per year in the placebo vs 0.03 per year in the Pembrolizumab arm, during the first year, and it will be 0.015 subsequently, in both arms, and if alternative hypothesis H1 (actual treatment HR=0.7) is true, the required 409 RFS events will be reached after a subsequent follow-up of approximately 12 months (i.e. approximately 3.0 years from the start of the trial). Approximately 6-9 months thereafter, once the data are complete and correct, the data-base will be locked, the final analysis for RFS will be performed.

RFS for the PD-L1+ subgroup is the other main endpoint of this study. The power is presented for the PD-L1+ subgroup where the events in the subgroup range from 30%-60% of the 409 overall RFS events, the subgroup HR=0.55, 0.6, 0.65, or 0.7 and alpha is allocated or alpha=0.025 (see Table 12). Under these scenarios, the power for the subgroup ranges from 41% to 100%. Finally the power for rejecting the RFS hypothesis for either the PD-L1+ subgroup or overall is presented. Under these scenarios, the power for rejecting at least 1 RFS hypothesis is at least 93%.

Endpoint: RFS for the PD-L1+ Subgroup					
% Events PD-L1+	Allocated Alpha†	HR	% Power (alpha=allocated)†	% Power (alpha=0.025) ††	% Power reject at least 1 RFS Hypothesis
30 (123/409)	0.0134	0.55	86	91	96
		0.6	73	81	95
		0.65	57	66	93
		0.7	41	50	93
40 (164/409)	0.0143	0.55	95	97	98
		0.6	86	90	96
		0.65	71	79	94
		0.7	54	63	93
50 (205/409)	0.0154	0.55	98	99	99
		0.6	93	95	97
		0.65	82	87	94
		0.7	65	72	93
60 (245/409)	0.0167	0.55	99	100	100
		0.6	97	98	98
		0.65	89	92	95
		0.7	75	80	93

Endpoint: RFS for the PD-L1+ Subgroup					
% Events PD-L1+	Allocated Alpha†	HR	% Power (alpha=allocated)†	% Power (alpha=0.025) ††	% Power reject at least 1 RFS Hypothesis
According to the multiplicity strategy (Bonferroni-Holm), the hypothesis for the overall population will first be tested at alpha=1.4%. † According to the multiplicity strategy, RFS for the PD-L1+ subgroup will be tested at the allocated alpha if the RFS hypothesis for the overall population is not rejected at alpha=0.014. †† According to the multiplicity strategy, RFS for the PD-L1+ subgroup will be tested at alpha=0.025 if the RFS hypothesis for the overall population is rejected at alpha=0.014. If the hypothesis for the PD-L1+ subgroup is rejected at the allocated alpha (alpha in parentheses), then the hypothesis for the overall population will be tested at alpha=2.5%					

Table 12: Estimations of RFS events in PD-L1+ Subgroup

One interim analysis is planned for assessing whether pembrolizumab is superior to placebo with respect to the improvement of RFS in the overall population. The interim analysis will occur after approximately 330 RFS events have been reported, and will be based on the primary efficacy analysis on the primary efficacy population (ITT population). Additional details regarding the interim analysis can be found in Section 8.3 (Interim analyses) of the protocol.

After the RFS final analysis, patients will continue to be followed for the efficacy endpoints: RFS (for those still alive and disease-recurrence free), DMFS (for those still alive and distant -metastasis free) and OS (for those still alive).

DMFS is a secondary endpoint of this study. In case the treatment comparisons regarding RFS and RFS in the PD-L1+ subgroup are both significant, DMFS (and DMFS in the PD-L1+ subgroup) will be tested (see Table 13).

	Endpoint: DMFS **Hazard ratio (HR) = 0.725, 1-sided alpha=1.4%, power=87%** **Hazard ratio (HR) = 0.725, 1-sided alpha=2.5%, power=91%**							
	Expected DMFS rate at			**Hazard rate (lambda) per year**				**Total nb. of pts: 900**
	1-yr	4-yr	7-yr	<=1 yr	1-<4 yr	4+ yrs	Total nb. of DMFS Events	100 pts/first 6 months 200 pts/month 7-12 600 pts/2nd year
Placebo	70.5%	44.9%	40.0%	0.35	0.15	0.0385	423	Accrual: 2 years ± additional follow-up: 3.1 years ± total follow-up: 5.1 years
Pembrolizumab	77.6%	55.96%	51.5%	0.2538	0.109	0.0279		
Difference/HR	7.1%	11.06%	11.5%	0.725	0.725	0.725		

Table 13: Estimations of DMFS events

DMFS for the PD-L1+ subgroup is another secondary endpoint of this study. The power is presented for the PD-L1+ subgroup where the events in the subgroup range from 30%-60% of the 423 overall DMFS events, the subgroup HR=0.55, 0.6, 0.65, or 0.725, and alpha is allocated or alpha=0.025 (see Table 14). Under these scenarios, the power for the subgroup ranges from 34% to 100%. Finally the power for rejecting the DMFS hypothesis for either the PD-L1+ subgroup or overall is presented. Under these scenarios, the power for rejecting at least 1 DMFS hypothesis is at least 88%.

Endpoint: DMFS for the PD-L1+ Subgroup					
% Events PD-L1+	Allocated Alpha†	HR	% Power (alpha=allocated)†	% Power (alpha=0.025) ††	% Power reject at least 1 DMFS Hypothesis
30 (127/423)	0.0134	0.55	88	92	95
		0.6	75	82	92
		0.65	58	68	90
		0.725	34	44	88
40 (169/423)	0.0143	0.55	96	97	97
		0.6	87	91	94
		0.65	73	80	91
		0.725	46	55	88
50 (212/423)	0.0154	0.55	99	99	99
		0.6	94	96	96
		0.65	83	88	92
		0.725	57	65	88
60 (254/423)	0.0167	0.55	100	100	100
		0.6	97	98	98
		0.65	90	93	94
		0.725	67	73	88
† According to the multiplicity strategy, DMFS for the PD-L1+ subgroup will be tested at the allocated alpha if the DMFS hypothesis for the overall population is not rejected at alpha=0.014. †† According to the multiplicity strategy, DMFS for the PD-L1+ subgroup will be tested at alpha=0.025 if the DMFS hypothesis for the overall population is rejected at alpha=0.014.					

Table 14: Estimations of DMFS events in PD-L1+ Subgroup

After the DMFS final analysis, patients will continue to be followed for the efficacy endpoints: RFS (for those still alive and disease-recurrence free), DMFS (for those still alive and distant -metastasis free) and OS (for those still alive).

OS is a secondary endpoint of this study. In case the treatment comparisons regarding DMFS and DMFS in the PD-L1+ subgroup are both significant, OS (and OS in the PD-L1+ subgroup) will be tested.

Assuming that the median survival post a RFS event is 1.64, approximately 30% of patients will still be alive 3 years post a RFS event (see Table 15).

In order to detect an OS HR=0.75 with 80% power a total of 380 deaths are required. After a 2-year accrual period and based on the scenarios indicated above regarding RFS results, approximately 520 RFS events will be reported after 3 years of additional follow-up, and 540 RFS events one year later. Therefore, given that 70% of patients with an RFS are expect to die within 3 years, a total of 380 deaths could be reached within 8-8.5 years from the start of the accrual.

Assuming a piece wise exponential distribution in the placebo randomized arm, i.e. OS hazard rates of 0.026 pre-0.5 year, of 0.161 per year, post-0.5 year till year 3, of 0.0912 per year during year 3 till 5, and 0.026 per year thereafter, the OS comparison will be powered to detect a treatment HR of 0.75, corresponding to an increase of the 3-year OS rate from 66.0% to 73.2% and of the 5-year OS rate from 55% to 63.9%. The power could also be 73% according to the multiplicity strategy which allocates alpha=1.4% to OS (discussed below).

	Endpoint: OS **Hazard ratio (HR) = 0.75 , 1-sided alpha=1.4%, power=73%** **Hazard ratio (HR) = 0.75 , 1-sided alpha=2.5%, power=80%**								
	Expected OS rate at			**Hazard rate (lambda) per year**					**Total nb. of pts: 900**
	0.5 yr	3 yrs	5 yrs	<=0.5 yr	0.5 - <3 yrs	3-<5 yrs	5+ yrs	Total nb. of deaths	100 pts/first 6 months 200 pts/month 7-12 600 pts/2nd year
Placebo	98.7%	66.0%	55.0%	0.026	0.161	0.0912	0.026	380	Accrual : 2 yrs ± additional follow-up: 6.5 years ± total follow-up: 8.5 years
Pembrolizumab	99.0%	73.2%	63.9%	0.019	0.121	0.068	0.0195		
Difference/HR	1.3%	7.2%	8.9%	0.75	0.75	0.75	0.75		

Table 15: Estimations of OS events

The analysis of OS will be performed once 380 deaths have been reported, i.e. approximately 7.0 years from the trial inception, if H1 is true (actual treatment HR=0.75), and considering that the drop out hazard rate will be 0.015 per year in the placebo vs 0.03 per year in the Pembrolizumab arm, during the first year, and it will be 0.015 subsequently, in both arms.

In case the HR=0.8 (i.e. lower randomized treatment difference regarding OS due to a larger impact of the crossover on OS post-recurrence), 380 deaths will provide a power for detecting a treatment difference of approximately 56% (1-sided alpha=2.5%). In case the HR is as high as 0.90, the power will be 16% (1-sided alpha=2.5%).

OS for the PD-L1+ subgroup is another endpoint of this study. The power is presented for the PD-L1+ subgroup where the events in the subgroup range from 30%-60% of the 380 OS events, the subgroup HR=0.6, 0.65, 0.7, or 0.75, and alpha is allocated or 0.025 (see Table 16). Under these scenarios, the power for the subgroup ranges from 70% to 97% (if HR=0.6) and from 25% to 58% (if HR=0.75). Finally the power for rejecting the OS hypothesis for

either the PD-L1+ subgroup or overall is presented. Under these scenarios, the power for rejecting at least 1 OS hypothesis is at least 74%.

Endpoint: OS for the PD-L1+ Subgroup					
% Events PD-L1+	Allocated Alpha†	HR	% Power (alpha=allocated)†	% Power (alpha=0.025) ††	% Power reject at least 1 OS Hypothesis
30 (114/380)	0.0134	0.6	70	78	84
		0.65	53	63	80
		0.7	38	48	76
		0.75	25	34	74
40 (152/380)	0.0143	0.6	83	88	89
		0.65	68	76	83
		0.7	50	59	78
		0.75	34	43	75
50 (190/380)	0.0154	0.6	91	94	93
		0.65	79	84	86
		0.7	62	69	79
		0.75	43	51	75
60 (228/380)	0.0167	0.6	96	97	96
		0.65	87	90	89
		0.7	71	77	81
		0.75	52	58	76
† According to the multiplicity strategy, OS for the PD-L1+ subgroup will be tested at the allocated alpha if the OS hypothesis for the overall population is not rejected at alpha=0.014.					
†† According to the multiplicity strategy, OS for the PD-L1+ subgroup will be tested at alpha=0.025 if the OS hypothesis for the overall population is rejected at alpha=0.014.					

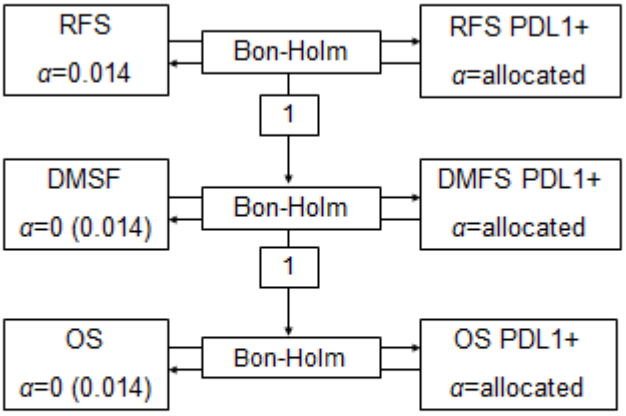
Table 16: Estimations of OS events in PD-L1+ Subgroup

The "graphical approach" (see Figure 5) to testing the hypotheses that the Pembrolizumab and placebo groups differ with respect to RFS, DMFS, OS and these endpoints in the PD-L1+ subgroup, will be adopted.

The initial 1-sided alpha allocation to RFS, DMFS and OS, will be 0.025, 0 and 0, respectively. This indicates that RFS, DMFS and OS will be tested sequentially. Both hypotheses (for the overall population and for the PD-L1+ subgroup) must be rejected to proceed to the next endpoint as indicated by the downward arrows and the boxed “1” indicating 100% of the alpha moves to the next endpoint.

For each endpoint, alpha allocation was determined as follows. For the overall population, 1-sided alpha=0.014. For the PD-L1+ subgroup, the allocated alpha will be calculated as a function of the event ratio (number of observed events in the PD-L1+ subgroup: total number of observed events) using a method by Spiessen and Debois. Several scenarios are discussed in the sample size calculation (above).

This "graphical approach" (see Figure 5) guarantees a 1-sided significance level of 0.025 for the study, as a whole. No multiplicity adjustment for other secondary analyses will be made.



Bretz, F., Maurer, W., Brannath, W. and Posch, M. (2009), A graphical approach to sequentially rejective multiple test procedures. *Statist Med* 2009, 28: 586–604.

Spiessens and Debois. Adjusted significance levels for subgroup analysis in clinical trials. *Cont Clin Trials* 2010; 31: 647–656.

Figure 5: Graphical approach

At the time of OS final analysis, an assessment of the long term treatment impact on RFS and DMFS will be evaluated as well.

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure). A minimization technique will be used for random treatment allocation stratifying by stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph

nodes vs. IIIC ≥4 positive lymph nodes) and region/country (North America, European countries, Australia and other countries as designated).

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

The main efficacy endpoints that will be used in the statistical analysis are listed in Section 2 and defined in Section 7.1.

8.2.2 Analysis populations

- Intention-to-treat (ITT) population: All randomized patients will be analyzed in the arm they were allocated by randomization.
- Per protocol treatment (PPT) population: All patients who are eligible and have started their allocated treatment (at least one dose of the study drug)
- Safety population: All patients who have started their allocated treatment (at least one dose of the study drug)

A patient will be considered to be eligible if he/she did not have any clinically relevant major deviations impacting efficacy analysis. Potential eligibility problems will be assessed by the Clinical Research Physician and Medical Review Team at time of medical review.

8.2.3 Statistical methods

8.2.3.1 Analysis methods for efficacy endpoints

All the main analyses of the efficacy endpoints (RFS, DMFS, OS) will be performed on the ITT population using the ITT principle: patients will be considered in the treatment group as indicated at randomization, regardless the "treatment" duration, cause of going off-protocol treatment, possible switch to another treatment before the 1st recurrence, etc.

The Kaplan-Meier technique will be used to obtain estimates of the survival-type distributions (RFS, DMFS, OS), and the standard error of the estimates will be computed using the Greenwood formula. Medians - if reached - will be presented with a 95% confidence interval based on the non-parametric method of Brookmeyer and Crowley.

The comparison of the time-to-event distributions (RFS, DMFS, OS) between the two treatment arms will be done using the log-rank test stratified by stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes), as indicated at randomization. The HR, and its (1-2xα)*100% confidence interval, of Pembrolizumab:Placebo, will be estimated using a Cox proportional hazards (PH) model (using Efron's tie-handling method), stratified by stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 nodes vs. IIIC ≥4 nodes) as indicated at randomization, with treatment as the single covariate.

8.2.3.2 Analysis methods for safety endpoints

No formal toxicity treatment comparison with p-values will be carried out.

8.2.4 Pre-planned sensitivity or exploratory analyses

8.2.4.1 Sensitivity analyses for efficacy endpoints (RFS, DMFS, OS)

For the efficacy endpoints, sensitivity analyses will be performed (see Table 17):

- to ensure true randomization via minimization, a re-randomization test will be performed:
  - RFS for ITT population
  - RFS for PD-L1+ ITT population
  - DMFS for ITT population
  - DMFS for PD-L1+ ITT population
  - OS for ITT population
  - OS for PD-L1+ ITT population
- using the ITT population, but considering the stratification factor (AJCC stage) information as indicated on the CRFs, based on pathology report(s) and applying the AJCC staging rules.
- using the PPT population.
- adjusting the treatment comparison by additional factors which appeared to be of prognostic importance (see below).
- In order to evaluate the robustness of the RFS endpoint, we will perform two sensitivity analyses with a different set of censoring rules (refer to the table below).

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No recurrence and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment	Recurrence at date of new anticancer treatment
Recurrence or death documented after ≤ 1 missed disease assessment	Recurrence at date of documented recurrence or death	Recurrence at date of documented recurrence or death	Recurrence at date of documented recurrence or death
Recurrence or death documented after ≥ 2 missed disease assessments	Recurrence at date of documented recurrence or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Recurrence at date of documented recurrence or death

Table 17: Sensitivity analyses

- In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we will also perform the following two additional RFS sensitivity analyses: 1) a RFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; 2) Finkelstein (1986)'s likelihood-based score test for interval-censored data, which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the RFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented recurrence and the right endpoint is the date of documented recurrence or death, whichever occurs earlier.

8.2.4.2 Exploratory analyses for primary and secondary efficacy endpoints (RFS, DMFS, OS)

Predictive importance of a factor (see list below), i.e. its impact on the treatment difference regarding the time to event end point (RFS, DMFS, OS) will be investigated for exploratory purposes. Consistency of treatment comparisons among subgroups of variables (see below) will be investigated using the Forest plot techniques. Subgroup analyses will be performed at 2-sided alpha=0.01 and 0.05. One should acknowledge the fact that the statistical power for the treatment comparisons will be limited in each subgroup. When interpreting the results of subgroup analyses, emphasis should be placed on the relevant tests for heterogeneity between subgroups, and not on the p-values obtained within the subgroups of all variables analyzed.

All subgroup analyses should be interpreted with caution and should be considered hypothesis-generating.

In addition, possible interactions between a factor and treatment effect will be assessed in a Cox model, in a bi-variate setting (i.e. treatment, variable, treatment x variable) and a multivariate one, i.e. adding in the model those factors which appear to be of independent prognostic importance (see below).

The PD-L1 patient distribution and magnitude of the treatment difference in the 2 main subgroups (PD-L1 positive vs PD-L1 negative) is unknown. So assuming:

- The prevalence of PD-L1 positive patients is 40%-60%,
- The treatment HR is 0.7 in the overall population,
- PD-L1 status has no prognostic importance in the placebo arm, i.e. 3-yr RFS (PD-L1+) = 3-yr RFS (PD-L1-) = 35.3%,
- PD-L1 status has prognostic importance in the Pembrolizumab arm: 3-yr RFS (PD-L1+) = 56.4%,
- In PD-L1-positive expression, the treatment HR = log(.564)/log(.353) = 0.55, and
- In PD-L1-negative expression, the treatment HR is 0.95-1.00.

	Prevalence PD-L1+/Prevalence PD-L1- in the entire cohort			
Pembrolizumab arm	40%/60%	50%/50%	55%/45%	60%/40%
3-yr RFS (PD-L1-)	42.5%	39.5%	37.6%	35.1%
HR in PD-L1-	0.82	0.89	0.94	1.00
Power for the treatment - PD-L1 interaction	48.9%	66.9%	76.3%	83.9%
Study number of events	409	410	409	409
Number of events for an 80% power for the treatment - PD-L1 interaction	825	554	447	370

Table 18: Prevalence PD-L1+/Prevalence PD-L1- in the entire cohort

So assuming the prevalence of PD-L1 positive patients is 40%-60% and the treatment HR is 0.55 in PD-L1 positive patients vs. 0.95-1.00 in PD-L1 negative patients, this large study is sufficiently powered to detect an interaction between PD-L1 expression and treatment difference regarding RFS, at the time of the final analysis, when 409 RFS events will be reported (see Table 18).

This PD-L1 expression interaction test is exploratory. These results will not supersede the PD-L1+ subgroup primary analysis for RFS and secondary analysis for DMFS and OS.

8.2.4.3 Exploratory analyses for exploratory efficacy endpoint (PRFS2)

The main analysis of this endpoint (PRFS2) will be performed on the ITT population using the ITT principle: patients will be considered in the treatment group as indicated at randomization, regardless the "treatment" duration, cause of going off-protocol treatment, possible switch to another treatment before the 1st recurrence and/or before the progression or 2nd recurrence.

The Kaplan-Meier technique will be used to obtain estimates of the survival-type distributions (PRFS2), and the standard error of the estimates will be computed using the Greenwood formula. Medians - if reached - will be presented with a 95% confidence interval based on the non-parametric method of Brookmeyer and Crowley.

8.2.5 Prognostic factor analyses

The following variables will be considered for the efficacy endpoints (RFS, DMFS, OS):

- PD-L1 expression (negative vs positive vs undetermined).
- Variables considered in the AJCC Staging:
  - LN involvement: micro vs. macro- involvement
  - Ulceration: absent vs. present vs. unknown
  - Number of lymph-nodes positive: 1 vs. 2-3 vs. 4+
- Breslow thickness (< 2 mm vs 2-<4 mm vs ≥4 mm)
- BRAF-mutation status (negative vs positive vs unknown)
- Sex (Male vs. Female)
- Age (at randomization <65 vs. ≥65 yrs)

Other variables might also be assessed based on new information that may become available during the course of the study.

In order to avoid a possible treatment influence on the prognostic importance of these factors, univariate analyses (Kaplan-Meier curves, logrank test, Cox model) will be done in each treatment group, separately.

Thereafter a multivariate Cox model will be fitted using both treatment groups, including as covariates randomized treatment group and all factors which appeared of prognostic importance in univariate analyses. A step down and step-up procedure will be used for the multivariate model selection at the 2-sided 5% significance level, and forcing treatment arm to stay in the model. The model with the lowest Akaike information criterion (AIC) will be retained. Such analysis of the treatment comparison adjusted by prognostic factors will be considered as a sensitivity analysis of the main one (see Section 8.2.4). The assumption of proportional hazards will be checked using a procedure derived from cumulative sums of martingale-based residuals over follow-up time (method of Lin, Wei, and Ying). In case one

of the strong prognostic factors will violate the PH assumption, a Cox model stratified by this factor will be considered.

8.2.6 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (e.g., re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

One interim analysis is planned for assessing whether pembrolizumab is superior to placebo with respect to the improvement of RFS in the overall population. The interim analysis will occur after approximately 330 RFS events have been reported, and will be based on the primary efficacy analysis on the primary efficacy population (ITT population). An unblinded statistician not connected with the project will perform the interim analysis so that the project statistician can remain blinded until the time of the final RFS analysis. The final RFS analysis will either occur immediately after the interim analysis is performed (if superiority is concluded at the time of the interim analysis) or after 409 RFS events have been observed (if superiority is not concluded at the time of the interim analysis). The EORTC Independent Data Monitoring Committee (IDMC) will review the analysis results and recommend whether the study should continue as planned or if there is sufficient evidence to conclude

that pembrolizumab is superior to placebo with respect to the improvement of RFS in the overall population. The stopping boundaries for the interim analysis will be based on the O'Brien-Fleming spending function.

The final RFS analysis will be performed with early rejection of the null hypothesis (i.e., pembrolizumab is superior to placebo with respect to the improvement of RFS in the overall population) if the test statistic crosses the pre-specified stopping boundaries (i.e., the value of the test statistic is greater than the value of the O'Brien-Fleming stopping boundary at the time of the interim analysis, suggesting that pembrolizumab is superior to placebo).

Table 19 displays the operating characteristics of the interim analysis, in case 330 RFS events have been reported, superiority would be concluded if the observed RFS hazard ratio is ≤ 0.76.

Power (%) to detect a HR=0.7 (overall 1-sided alpha=0.014)	91.4
# of events (interim)	330
p-value to show superiority (interim)	≤0.006
p-value to show superiority (final)	≤0.012
Observed HR to show superiority (interim)	≤0.76
Observed HR to show superiority (final)	≤0.8
Probability (%) of superiority (interim)	77.1
Probability (%) of superiority (final, if superiority not detected at interim analysis)	14.3
Probability (%) no superiority (final)	8.6

Table 19: Operating Characteristics of the Interim Analysis

The O'Brien-Fleming stopping boundary at the interim analysis using Lan-DeMets alpha spending function will be derived based on the exact number of reported RFS events. EAST 6.4 program will be used.

In terms of analysis, the statistical methods described in 8.2.3 will be used for the interim analysis. However, the (1-2xα)*100% confidence interval of the Pembrolizumab:Placebo HR will be computed using the 1-sided alpha error "adjusted" by the interim look (e.g. 0.006, in case 330 RFS events were reported at the time of interim analysis for the overall population).

If, at the time of the interim analysis, pembrolizumab is shown to be superior to placebo with respect to the improvement of RFS in the overall population, then the multiplicity strategy will be carried out as described in Section 8.1.1 (i.e. using a 1-sided alpha=0.014). If pembrolizumab is not shown to be superior to placebo at the time of the interim analysis, then the multiplicity strategy will be carried out using a 1-sided alpha=0.012 (rather than 0.014).

See section 9 for interim safety monitoring.

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment

2. The trial is mature (i.e. reached the required number of events) for the 3 final analyses of the efficacy endpoints as defined in the protocol: one for RFS (overall, and in PD-L1-positive expression), one for DMFS (overall, and in PD-L1-positive expression) and one for OS (overall, and in PD-L1-positive expression).

3. The database has been fully cleaned and frozen for all of these 3 final analyses.

4. As in other EORTC melanoma adjuvant trials, a very long term follow-up, when all patients have a 10-year follow-up is foreseen.

9 Data Monitoring

9.1 Safety data monitoring

The EORTC Independent Data Monitoring Committee (IDMC) will review safety information at six monthly intervals or when appropriate.

The Study Steering Committee will not review safety information. For the Trial Steering Committee members and role refer to Steering Committee Charter.

Unblinding for global safety reasons and unblinding at interim safety analyses will be performed according to EORTC SOP CM-011-SOP “Blind Studies”. The unblinded Statistician, an independent Statistician at the EORTC Headquarters not involved in the conduct of the trial and the Pharmacovigilance Physician will write the unblinded safety interim report and will present it to the IDMC.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

9.2 Efficacy data monitoring

In general, the EORTC IDMC is charged with the interim review (planned in the protocol or ad hoc) of randomized phase II and phase III studies. When interim analyses are carried out, the interim monitoring of efficacy and safety data is performed according to the Statistical Considerations chapter in this protocol and EORTC Policy 004 on “Independent Data Monitoring Committees and Interim Analyses”.

In the present study, an interim analysis will be performed after approximately 330 RFS events have been documented. The IDMC will independently review the interim analysis following the EORTC POL004 (for more details see chapter 8.3).

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study (protocol).

No efficacy results will be presented at EORTC Group meetings or elsewhere, before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Quality of life assessment

10.1 Rationale

HRQoL is a multidimensional construct, which can be defined as a state of general wellbeing reflecting physical, psychological, and social wellbeing and the impact of the disease and/or treatment related symptoms on daily-life functioning. The patient's subjective perspective is an inherent component of HRQoL and is therefore best assessed via self-administration.

Reducing mortality and morbidity is still the most important factor in cancer clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients' satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish a patient's quality of life even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their HRQoL consequences.

Patients with resected stage III melanoma report good and stable overall HRQoL during the subsequent years after resection. Adjuvant treatment (such as interferon) can however interfere through side effects on the patients functioning. In this study, QoL is an exploratory endpoint. The main objective of HRQoL assessment within this clinical trial is to determine the impact of adjuvant immunotherapy versus placebo. The primary HRQoL endpoint will be overall health/QoL. Patients undergoing adjuvant immunotherapy may experience reduction in overall HRQoL due to side effects such as fatigue, nausea, pruritus, diarrhea and rash.

The primary hypothesis is we expect no clinically relevant differences between the two treatment arms using the global QoL scale during the first two years. To meet this objective QoL questionnaires will also be administered after progression. Secondary objectives include evaluation of the effect of adjuvant immunotherapy specifically during the treatment period.

10.2 Objective

The primary hypothesis is we expect no clinically relevant differences between the two treatment arms using the global QoL scale during the first two years. To meet this objective, QoL questionnaires will also be administered after recurrence/progression. Secondary objectives include evaluation of the effect of adjuvant immunotherapy specifically during the treatment period.

10.3 HRQoL instrument

No validated immune-specific questionnaires for use in oncology trials exist. Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This instrument is composed of multi-item and single-item scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single

items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups (Ref. 64). The average time to complete the questionnaire is approximately 10 minutes.

The EORTC QLQ-C30 version 3 has been translated in over 50 languages according to a standardized translation procedure.

The domains of interest as specified in the previous paragraph are covered by global health/QoL scale. The other scales will be considered secondary.

10.4 Study design

HRQoL questionnaires must be filled out at the hospital when patients come for a scheduled visit according to the EORTC "Guidelines for administration of questionnaires" (see Appendix D). The pre-treatment questionnaires must be filled at baseline (within 6 weeks before randomization). Subsequent questionnaires are filled in every 12 weeks after the first study drug treatment for the first two years. HRQoL data must be collected regardless of the patient's recurrence/progression status, unless patient withdraws from this part of the study.

Master copies of the HRQoL questionnaires will be sent to the institutions. Additional copies or translations can be provided upon request via the EORTC contact person. The clinical report forms will include a question whether the HRQoL forms have been filled in, and if not, the reason why. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. The patient should complete the questionnaires by her/himself in her/his own language during the visit to the outpatient clinic as completely and accurately as possible. It is recommended that a key person (e.g. research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

During the study, compliance with completing questionnaires will be investigated at each time point. The compliance of the HRQoL assessments will also be reviewed twice a year and will be part of the descriptive report.

10.4.1 HRQoL schedule

The time windows for eligible HRQoL (EORTC QLQ-C30 and EQ-5D-3L) assessments will be as follows (see Table 20):

Assessment	Time window
Baseline	Can be completed before or on the day of randomization itself but no earlier than 6 weeks before.
Every 12 weeks (during year 1 and 2 after randomization)	At week 12, 24, 36, 48, 60, 72, 84, 96, 108. Can be completed up to 2 weeks before or after the intended visit date.
Every 6 months (during year 3 and 4 after randomization)	At month 30, 36, 42 and 48. Can be completed up to 6 weeks before or after the intended visit date.

Table 20: HRQoL schedule

Note: A maximum of 14 assessments per patient are required, namely: baseline, week 12, 24, 36, 48, 60, 72, 84, 96, 108, month 30, 36, 42 and 48. At each scheduled visit, EQ-5D-3L will be collected prior to EORTC QLQ-C30. Refer to "Guidelines for administration of questionnaires". These data must be collected regardless of the patient's recurrence/progression status, section 6.3.4.3 for this part of the study.

10.5 Statistical considerations

The primary HRQoL endpoint that is considered relevant for this study is the global health/QoL scale. The other available scales will only be analyzed on a descriptive basis.

A difference of 10 points on the 100-point QLQ-C30 scale between the two arms will be considered as clinically relevant. The standard deviation of this scale is approximately 20 points. With the 2-sided alpha set at 5% and a power of 80% to detect a difference of 10 points (effect size of 0.5), a minimum of 128 patients (64 per treatment arm) is required. For an effect size of 0.75 (difference of 15 points), 56 patients (28 per treatment arm) are required. Therefore, this study is sufficiently powered to detect differences in HRQoL.

Data will be scored according to the algorithm described in the EORTC scoring manual. All scales and single items are scored on categorical scales and linearly converted to 0-100 scales.

The QoL scores in the two arms will be compared by using summary statistics. Three summary statistics will be calculated per patient:

- The average change from baseline reported during the first four years.
- The average change from baseline reported during treatment (up to 21 days after last administration).
- The average change from baseline reported after treatment (from 21 days after last administration until four years).

Non-parametric rank-order tests will be performed using a two-sided significance level of 5% to test for significant differences between the treatment arms. Change from baseline per timepoint will be reported in a descriptive manner to provide support for the main results.

An overall effect of the treatment on the QoL scores will be determined primarily on the basis of the primary analysis. Because the study is overpowered, both statistical significance and the treatment effect size of clinical relevance on the QoL scores should be taken into consideration. Differences will only be considered as clinically relevant if they exceed the 10-point threshold. The proportion of patients experiencing a clinical relevant change will be calculated as well per summary statistic.

For all quality of life domains and items, cross-sectional descriptions of the average scores will be presented by treatment arm at each time point of assessment together with confidence intervals and a graphical display of the patterns of change over time will be provided. The proportion of patients experiencing a clinical relevant deterioration per scale will be provided as well.

10.5.1 Missing data

Missing data is a potential major source of bias in HRQoL assessment.

In order to check the potential impact in the study, the compliance mechanism will be investigated prior to initiating the HRQoL analysis. Compliance by instrument, visit and treatment arm will be described by absolute number and relative percentage. Compliance rate is defined as the proportion of valid forms received versus the number expected.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the results vis-à-vis the missing data. Missing values will be imputed via various linear regression models. These completed data will be analyzed similar to the main method as sensitivity analyses to assess the stability of the main results vis-à-vis the missing data.

In case overall compliance is deemed too low (<50%), only an exploratory analysis will be performed in lieu of the main analysis.

10.6 Health outcomes evaluation

10.6.1 EQ-5D-3L instrument

The EQ-5D-3L is a general health status and health utility measure (Ref. 65). It measures 5 dimensions of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression each assessed by a single question on a three-point ordinal scale. It also includes a VAS scale to measure health state. The EQ-5D will be included in this study for the purpose of the computation of utilities that can be used in health economic studies. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability (Ref. 66). In addition, validated translations for this instrument are available for a number of countries and languages (Appendix M).

The assessment schedule of the EQ-5D-3L is identical to the schedule of the QoL instrument (QLQ-C30) as described in 10.4.1.

11 Pharmacokinetic/Pharmacodynamic Evaluations

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, samples will be collected for analysis of anti-drug antibodies (ADA) and PK.

Based on pharmacokinetic (PK) data obtained in this study as well as PK data obtained from other studies (if available), a population PK analysis will be performed to characterize pharmacokinetic parameters (Clearance (CL), Volume of distribution (V)) as endpoints and evaluate the effect of extrinsic and intrinsic factors to support proposed dosing regimen. Pharmacokinetic samples will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical trials, it may be decided to discontinue further sample collection or analysis in this study.

11.1 Timepoints

Sample collection is currently planned as shown in Section 6.4.3.

11.2 PK Blood Collection for Serum MK-3475

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

11.3 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for anti-pembrolizumab antibody samples will be provided in the Procedures Manual.

12 Translational research

Overall Biobanking and Translational Research Study Coordinator:

PPD

Institut de Cancérologie Gustave Roussy
Villejuif, France

12.1 Objectives

In order to explore the biology of melanoma and in parallel assessing the prognostic and/or predictive value of potential biomarkers, this protocol includes a prospective biobanking for patients who have consented to take part in this research in view of translational research.

The objectives of this prospective biobanking are to prospectively collect biological material (whole blood, plasma, serum and tissue) for translational research projects for patients who have consented to take part in this research. Projects may include but are not restricted to:

- Targeted mutation analysis
- Targeted RNA expression analysis
- Liquid biopsies to monitor therapy response
- Immunohistochemistry

To ensure confidentiality, all samples and the information associated with the samples will be coded to prevent the exposure of subject information and identity. These evaluations are not expected to benefit the subject directly or to alter their treatment course. The results will not be communicated or placed in their medical record and will not be made available to members of their family, treating physicians, or other third parties except as specified in the informed consent

12.2 Patient selection criteria

- Signed "Biobanking" informed consent.
- Eligible for and enrolled in EORTC-1325-MG study.

12.3 Biological material

Tumor tissue will be collected from positive lymph nodes. Lymph nodes embedded in paraffin will be banked for studies of additional correlates of response.

Primary melanoma may also be collected if available and used for additional correlative analyses.

Samples collection (whole blood, plasma, serum and tissue) is currently planned as shown by the Trial Flowchart see Section 6.4.3. Sample collection, storage and shipment instructions for TR samples will be provided in the Procedures Manual.

12.4 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Bioinformatics and statistical analysis plan will be jointly developed for each project. These documents will be developed and approved before starting any analysis. They will specify the analytical and methodological details. Clinical and patient-reported outcome data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating institutions. Transfer of data will be performed according to applicable policies in each organization (e.g. EORTC POL008) or according to jointly approved data transfer charters.

12.5 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

In this study, biological material for translational research will be centralized and stored at Institut de Cancérologie Gustave Roussy, Paris, France. The biobank will perform the above research project as stated in the protocol. In addition the biobank will distribute HBM to the other research laboratories involved in the translational research (TR) projects that will be defined in the future.

The following principles apply to storage of HBM:

- The collected HBM should be documented, i.e. the amount remaining and its location.

The study chairman (SC) and the study coordinator (SC) will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol.

Access to HBM is defined by the EORTC Biobanking Policy POL020 and will follow the next steps:

A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with SCs.

- The SCs will prioritize the TR projects. Access procedures defined by the SCs will build on the following key points:
  - Project prioritization
    - should be strongly based on scientific merit,
    - should consider the contribution of the different investigators to the trial and TR project,
    - will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).
  - Protection of confidentiality must be respected.
- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.
- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).
- Once SCs prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SCs and the TR project leader(s), as needed.

13 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once the following documents have been provided:

- The updated signed and dated curriculum vitae of the Principal Investigator in English with a GCP training proof.
- The (updated) list of normal ranges for the investigator's institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- The Confirmation of interest, confirming that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared.

- The Study Agreement with investigator's institution.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be provided.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to register/randomize patients in the trial as soon as

- All the above mentioned documents are collected.
- All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

14 Patient registration and randomization procedure

14.1 General procedure

Investigator will register and enroll patients during screening through EORTC, following the standard EORTC procedure. Patient registration and randomization will only be accepted from authorized investigators (see Section 13 on “investigator authorization procedure").

Patients should be registered directly on the **EORTC online system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to register patients via the EORTC call center. Registration via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be) and it is updated annually.

Through Internet: http://orta.eortc.be
In case of problems registration by phone: PPD

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

The study is referred as EORTC-1325 and MK-3475-054. However, in order to ease the registration process, the protocol number will be entered as 1325 at each step of the process below.

In order to protect patients’ privacy when required by local regulations, clinical sites will report the day/month of birth as 01-January.

14.2 Registration - step 1 (ORTA Step-1)

Patient registration will only be accepted from authorized investigators.

A patient can only be registered after signature of the Patient Informed Consent for tumor testing and fulfillment of all criteria listed in protocol section 3.1. Patients who are not eligible for registration will not be assigned a patient identifier and no information will be recorded in the database.
A short list of questions needs to be answered during the registration (step 1). Those questions are included in the Registration Form, which is part of the case report forms.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number: 1325
- step number: 1

- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics, a unique code to help identify the patient within your institution*)
- patient's birth date (*day/month/year*) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- date of written informed consent for tumor testing (*day/month/year*)

A **sequential patient identification number ("seqID")** will also be assigned at the end of the registration procedure.The seqID will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

Note: A patient who is ineligible during initial screening assessments, may be re-screened by starting a new registration and a new sequential identification number will be assigned.

14.3 Central confirmation of PD-L1 expression testing - step 2

The outcome of the central confirmation will be provided to clinical site after patient has been registered (step 1). Clinical site must enter PD-L1 eligibility status in ORTA prior to proceeding to step 3.

14.4 Enrollment and Randomization - step 3 (ORTA Step-2)

After registration (step 1), the central laboratory will confirm the results of the PD-L1 status testing (step 2)

A patient can only be enrolled after verification of eligibility.

An exhaustive list of questions to be answered during the enrollment procedure.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number: 1325
- step number: 2
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics, a unique code to help identify the patient within your institution*)
- patient's birth date (*day/month/year*) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- result of the PD-L1 expression test
- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- stratification factors
- date of written informed consent to participate in the trial (*day/month/year*)
- TNM stage

At the end of the randomization procedure, the treatment will be randomly allocated to the patients (minimization technique) through the IVRS system. As this is a double blind trial, neither the treatment arm nor its description will be provided to the investigator, the Sponsor, EORTC staff, CRO, patients and site staff.

The local pharmacists and limited CRO personnel will be unblinded.

14.5 Description of the blind procedure

The IVRS system will assign to each patient a treatment dynamically, based on the other patients randomized in the study and the stratification factors defined in the protocol. The treatment arm will be blinded for patients participating in Part 1 of the study until first recurrence.

14.6 Stock management process

The stock of pembrolizumab is maintained in each institution participating in the protocol with the help of the IVRS system for both ongoing and new patients.

The institution needs to confirm to the IVRS system the reception of each shipment of pembrolizumab before it can be allocated to patients.

14.7 Unblinding procedure

The following are expected authorized unblinding events in the study:

- Emergency unblinding
- Unblinding by investigator after first disease recurrence
- Unblinding at final analysis
- Other unblinding during the course of the study

14.7.1 Emergency unblinding

At any time during the trial, in case of a safety concern affecting an individual patient, the site investigator can request the unblinding of that patient.

The unblinding requests should be made by the site investigator through the emergency unblinding call center. Alternatively, a health care provider can obtain information about the

trial medication in emergency situations where the investigator is not available, as per section 6.1.1.

The emergency unblinding call center will use the randomization schedule for the trial to unblind patients and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS) should be used in order to unblind patients and to unmask treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary.The system will ask the reason why the treatment needs to be unblinded. If the reason given justifies unblinding, an automatic email describing the unblinded treatment will be sent to the investigator.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. The principal investigator or delegate and the respective patient will be unblinded. If other trial site personnel, EORTC HQ (except the statistician), Sponsor personnel or Covance study teams become unblinded to assist the case, it is acceptable and not considered an inadvertent unblinding incident due to the emergency unblinding.

14.7.2 Unblinding by investigator after first disease recurrence

The investigator will request authorization for official unblinding upon disease recurrence and consideration to proceed to Part 2 of the study (Cross-over or Re-challenge treatment).

The emergency unblinding methods described in Section 14.7.1 should not be used in this process.

During the study, all data must be entered in the eCRF within 5 days of each patient's visit. Upon first recurrence, every effort will be made to have all pending data entered into the eCRFs within 1 business day or before the site is unblinded to the patient's treatment assignment.

The site should ensure data for disease recurrence is entered in the database prior to unblinding. Additionally, any AEs and/or Serious AEs should be reported and causality attributed in the database prior to unblinding. Please refer to the CRF guidelines and contact the site monitor for operational details. The site will request a unique unblinding code to the EORTC Unblinding Mailbox PPD in order to proceed to unblinding via IXRS.

After unblinding is complete, the site will assess patient eligibility for Cross-over/Re-challenge by reviewing all qualifications per protocol Sections 4.2.1.1 and 4.2.2.1. If patient fulfills eligibility criteria, the site will access the recurrence phase module in IXRS and request treatment assignment in Part 2 of the study (Cross-over or Re-challenge treatment).

After disease recurrence, the study subject, investigator, site personnel, Sponsor personnel, EORTC HQ study team (except the statistician), and Covance study teams associated with the conduct of the trial will become unblinded in order to continue monitoring each patient in the study.

14.7.3 Unblinding at final analysis

The patient, the investigator and the site team and the EORTC HQ study team will be unblinded after database lock for the final analysis of the primary endpoint. At unblinding for final analysis, the project manager will inform investigators that the allocated treatment of their patients is available upon request.

Translational medicine studies will only be performed after unblinding for the primary endpoint

14.7.4 Other unblinding during the course of the study

Unblinding for the analysis planned in Section 8.3 and unblinding for global safety reasons are described in chapter 9.

Finally, unblinding may be required for the reporting of serious adverse events (SAEs) or pregnancies or submission of Development Safety Update Report (DSUR) to Competent Authorities, EudraVigilance Clinical Trial Module (EVCTM) and Ethics Committees. In this case, the patient, the investigator, the site team and the EORTC HQ study team remain blinded. The procedure is described in Section 16.7.

15 Forms and procedures for collecting data

15.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the QLQ-C30 form, the EQ-5D-3L form, the SAE/ECI form and the Pregnancy notification form which are paper CRFs.

Copies of the Quality of Life forms (QLQ-C30 and the EQ-5D-3L) should be sent directly to the EORTC Headquarters by one of the following means:

- By fax, to the attention of Melanoma Data manager: PPD
- By scanning and e-mailing the forms (see CRF completion guidelines)
- By post to the EORTC Headquarters:

(Melanoma 1325 Data Manager)

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

SERIOUS ADVERSE EVENTS (INCLUDING EVENTS OF CLINICAL INTEREST) AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see Section on Reporting Serious Adverse Events).

A. Before the treatment starts:

- The patient must be registered/randomized in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one hour after the registration/randomization on http://rdc.eortc.be/ or on http://www.eortc.org in the Section “Research tools”.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members with the exception of the paper **HRQoL** forms (no signature needed)

15.2 Data flow

The forms must be completed electronically, with the exception of the paper forms (the Quality of Life form, SAE form, Pregnancy notification form and EQ-5D-3L form), according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

A copy of the quality of life forms should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. If there are queries on the quality of life form, they will be raised electronically on a patient level in the VISTA/RDC system and they must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

Quality of life forms: If an investigator (or an authorized staff member) needs to modify the paper quality of life form after the copy has been sent to the EORTC Headquarters, he/she should create a request for data correction on a patient level in the VISTA/RDC system.

15.3 HBM* sample registration and tracking

Once the patient is registered, this procedure might take up to one hour, the investigator or his/her authorized staff must log on "Samples" website at https://samples.eortc.be/ or by clicking on the link "Samples Website" at the bottom of the page http://rdc.eortc.be

"Samples" is a web based tracking tool designed to register, manage and track Human Biological Materials collected in the frame of EORTC clinical trials.

Details about access the "Samples" Website, register samples and tracking shipments are described on the guidelines of HBM* management.

(*) Human Biological Material

16 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and Sponsor follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this Section of the protocol.

16.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: 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 unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.
- Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

ECI: The following **Events of Clinical Interest** should be reported as a SAE in an expedited way:

- Drug Induced Liver Injury (DILI): AST or ALT elevations ≥ 3 x ULN with concurrent elevation of total bilirubin ≥ 2 x ULN and, at the same time, alkaline phosphatase < 2 x ULN
- If grade ≥ Grade 2: Pneumonitis, Interstitial lung disease, Acute interstitial pneumonitis.
- If grade ≥ Grade 2: Nephritis, Autoimmune nephritis, Renal Failure, Acute Renal Failure
- If grade ≥ Grade 2 or any grade resulting in dose modification (please refer to protocol Appendix H) or use of systemic steroids to treat the AE: Intestinal Obstruction, Colitis, Colitis microscopic, Necrotizing colitis, Enterocolitis, Hemorrhagic enterocolitis, GI perforation, Diarrhea, Hepatitis, Autoimmune hepatitis, Transaminase elevations, Uveïtis, Iritis
- If grade ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification (please refer to protocol Appendix H) or use of systemic steroids to treat the AE: Adrenal Insufficiency, Hyperthyroidism, Hypothyroidism, Thyroid Disorder, Thyroiditis, Hypophysitis, Hypopituitarism

- If grade ≥ Grade 3 or any grade resulting in dose modification (please refer to protocol Appendix H) or use of systemic steroids to treat the AE: Autoimmune hemolytic anemia, Aplastic anemia, Thrombotic Thrombocytopenic Purpura (TTP), Idiopathic (or immune) Thrombocytopenia Purpura (ITP), Disseminated Intravascular Coagulation (DIC), Haemolytic Uraemic Syndrome (HUS), Creatinine elevations
- If grade ≥ Grade 3: Pruritus, Rash, Rash generalized, Rash maculo-papular, Any other Grade 3 (or higher) event which is considered immune-related by the physician
- If grade ≥ Grade 4: Any Grade 4 anemia regardless of underlying mechanism
- Regardless of grade: Dermatitis Exfoliative, Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Allergic reaction, Anaphylaxis, Cytokine release syndrome, Serum sickness, Infusion reactions, Infusion-like reactions, Autoimmune Neuropathy, Demyelinating Polyneuropathy, Guillain-Barre syndrome, Myasthenic syndrome, Myocarditis, Pericarditis, Pancreatitis, Any rash considered clinically significant in the physician's judgment

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

Overdose: For this trial, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of an overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

16.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by study treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.

- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

16.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc.

16.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in Table 21:

Relationship to the protocol treatment	**Description**
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

Table 21: Relationship to the protocol treatment

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

16.5 Expectedness assessment

The expectedness assessment is the responsibility of the Sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- For Pembrolizumab: Investigator's Brochure
- For Placebo: Safety Data Sheet

16.6 Reporting procedure for investigators

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 randomization/treatment allocation 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 randomization/treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Please refer to Section 16.2 for exceptions.

For the time period beginning when the consent form is signed until randomization/treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, 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.

All Serious Adverse Events (SAEs)/Events of Clinical Interest (ECI) occurring from the time a subject is randomized until 90 days after last blinded treatment administration (or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier) and to patients who continue or crossover to receive Pembrolizumab after first recurrence (i.e. patients with recurrence occurring more than 6 months after completion of 1 year (blinded) Pembrolizumab treatment or patients crossing-over from placebo), must be reported within 24 hours.

Any SAE/ECI that occurs outside of the SAE detection period and is considered to have a reasonable possibility to be related to the blinded treatment or study participation also needs to be reported to EORTC. SAEs/ECIs occurring to patients who continued or crossed-over to Pembrolizumab need to be sent until 90 days after last administration, thereafter only SARs need to be sent.

All SAEs must be followed up for outcome.

All SARs occurring to patients receiving investigator's choice of treatment (i.e. not Pembrolizumab) need to be reported to the Marketing Authorization Holder (MAH) of the administered drug(s).

Reporting schedule is detailed in Table 22.

Adjuvant part 1	Documents
Signed Patient Registration Informed Consent till randomization:	All SAEs* to EORTC
Randomization till 90 days after last blinded treatment administration:	All SAEs/ECIs to EORTC
From day 91 after last blinded treatment administration:	Only SARs/ECIs considered to have a reasonable possible relationship to blinded treatment/study participation to EORTC
After first recurrence part 2: for patients that will cross-over or be re-challenged	
Patients receiving Pembrolizumab after first recurrence till 90 days after last Pembrolizumab administration:	All SAEs/ECIs to EORTC
From day 91 after last Pembrolizumab administration (for patients after first recurrence):	Only SARs/ECIs considered to have a reasonable possible relationship to treatment/study participation to EORTC
After first recurrence for patients that will not cross-over or not be re-challenged	
if the subject initiates new anticancer therapy reporting till 30 days after last Pembrolizumab administration	All SAEs/ECIs to EORTC
From day 31 after last dose, all patients who receive new anticancer therapy after unblinding:	All SARs to MAH (**NOT** to EORTC)[for new anticancer therapy] All SARs/ECI considered to have a reasonable possible relationship to treatment/study participation to EORTC

Table 22: Reporting schedule

* if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention

Any secondary malignancy or second primary malignancy should also be reported in an expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed or emailed to:

EORTC Pharmacovigilance Unit:

Fax No. PPD

PPD

To enable the EORTC to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

16.7 Reporting responsibilities of the Sponsor

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at Merck as per Safety Data Exchange Agreement.

After receipt of the initial report, all information will be reviewed and, if necessary, the Investigator will be contacted to obtain further information for assessment of the event. The Sponsor will evaluate the seriousness and the causal relationship of the event to study medication. In addition, the Sponsor will evaluate the expectedness according to the reference safety information (see above). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

Unblinding may be required for the reporting of serious adverse events (SAEs) or pregnancies or submission of Development Safety Update Report (DSUR) to Competent Authorities, EudraVigilance Clinical Trial Module (EVCTM) and Ethics Committees. In this case, the patient, the investigator, the site team and the EORTC HQ study team remain blinded.

The EORTC Pharmacovigilance Unit and Merck have outlined the reporting of SUSARs in a Safety Data Exchange Agreement.

16.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 120 days after last protocol treatment administration, or within 30 days after last protocol treatment administration if new anticancer therapy is initiated (whichever is earlier), must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter
- 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.

17 Quality assurance

17.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

17.2 On-site quality control

Covance will periodically perform on-site quality control visits as as described in the Monitoring Plan: The first visit in a participating site will be performed within 2 months after the first patient's inclusion. Frequency of subsequent visits will depend on site's accrual and quality observed during the first visit.

17.3 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. In addition, Merck, as the protocol Sponsor, routinely conducts audits of participating investigator sites in accordance with the sponsor's approved audit plan. These audits are performed to provide assurance that the rights, safety and wellbeing of patients are properly protected, to assess compliance with the protocol,

processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, the Sponsor, any third party (e.g. a CRO) acting on behalf of the EORTC or the Sponsor, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant to the EORTC, the Sponsor, any third party (e.g. a CRO) acting on behalf of the EORTC or the Sponsor, direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: PPD .

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

18 Ethical considerations

18.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

18.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth or year of birth (as allowed per applicable legislation) will

also be reported on the case report forms. Day and month will be reported as 01-January to protect individual privacy if required by country local regulations.

18.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and, in some countries, it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

19 Administrative responsibilities

19.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

PPD
Institut de Cancérologie Gustave Roussy
114 Rue Edouard Vaillant, 94800 Villejuif, Paris, France
Phone:
Fax:
E-mail: PPD

Study chair

PPD
Institut de Cancérologie Gustave Roussy
114 Rue Edouard Vaillant, 94800 Villejuif, Paris, France
Phone:
Fax:
E-mail: PPD

19.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: PPD

19.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at PPD

EORTC Melanoma group

Chairman:

PPD
Institut de Cancérologie Gustave Roussy
114, rue Edouard Vaillant
94805 Villejuif CEDEX
France
Phone:
Fax:
e-mail: PPD

Secretary:

PPD
Department of Surgical Oncology
Netherlands Cancer Institute – PPD
Phone: PPD
Fax:
e-mail:

20 Trial sponsorship and financing

The legal Sponsor of this trial is Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co. Inc

One Merck Drive
P.O. Box 100
Whitehouse Station, NJ, 08889-0100, U.S.A.

21 Administrative and regulatory details

21.1 Confidentiality

21.1.1 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.

21.1.2 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.

21.1.3 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.

21.1.4 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.

21.2 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. 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.

21.3 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 Appendix L - 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 will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. 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 destroying 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.

21.4 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.

21.5 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.

21.6 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.

21.7 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 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
Drug administration equipment – as required for storing, preparing, and administering study treatment

22 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

23 Publication policy

The publication of the main trial results will be written by the Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters and will be sent to a major scientific journal. Authors of the manuscript will include at least the Study Coordinator, Study Chair, the investigators who have included more than 2.5% of the eligible patients in the trial (by order of inclusion), a minimum of two Merck representatives and a minimum of two members of the EORTC Headquarters team who have contributed to the trial.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment Section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as the trial Sponsor (Merck).

It is the EORTC’s policy not to release trial results before data maturity has been reached for the primary endpoint(s) of the trial unless the publication is authorized by the Data Monitoring Committee. If the group wishes to publish or present study data before the publication of the primary trial endpoint, this may be authorized under the conditions specified in the EORTC Policy 009 “Release of Results and Authorship Policy” available from http:\\www.eortc.be, or authorized by the Data Monitoring Committee.

The Group Chairman, the Study Coordinator, the Merck responsible(s) and the EORTC Headquarters Team must approve all publications, abstracts and presentations of data pertaining to patients included in this study.

The data collected during this study are confidential. Any publications or abstracts arising from this study require approval by the Sponsor prior to publication or presentation and must adhere to the Sponsor’s publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the Sponsor at the earliest practicable time for review, not less than 30 days before submission or presentation unless otherwise set forth in the CTA.

Sponsor shall have the right to delete any confidential information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

Appendix A: References

Ref. 1 Eggermont AMM, Spatz A, Robert C. Cutaneous Melanoma. Lancet. 2014 Mar 1;383(9919):816-27.

Ref. 2 Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009; 27: 6199–206.

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Ref. 4 Van Akkooi ACJ, Nowecki ZI, Voit C, et al. Sentinel node tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients: a multicenter study in 388 patients with positive sentinel nodes. Ann Surg 2008; 248: 949–55.

Ref. 5 Van der Ploeg APT, Van Akkooi ACJ, Rutkowski P, et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined Rotterdam tumor load and Dewar topography criteria. J Clin Oncol 2011; 29: 2206–14.

Ref. 6 van der Ploeg AP, van Akkooi AC, Haydu LE, Scolyer RA, Murali R, Verhoef C, Thompson JF, Eggermont AM. The prognostic significance of sentinel node tumour burden in melanoma patients: An international, multicenter study of 1539 sentinel node-positive melanoma patients. Eur J Cancer. 2014 Jan;50(1):111-20.

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Ref. 8 Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A, Grob JJ, Malvehy J, Newton-Bishop J, Stratigos A, Pehamberger H, Eggermont AM. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline--Update 2012. Eur J Cancer. 2012 Oct;48(15):2375-90.

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Ref. 10 Eggermont AM, Testori A, Maio M, Robert C. Anti-CTLA-4 antibody adjuvant therapy in melanoma. Semin Oncol. 2010 Oct;37(5):455-9.

Ref. 11 Wheatley K, Ives N, Hancock B, Gore M, Eggermont A, Suciu S. Does adjuvant interferon-alpha for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. Cancer Treat Rev 2003; 29: 241–52.

Ref. 12 Wheatley K, Ives N, Eggermont AMM, et al. Interferon-α as adjuvant therapy for melanoma: An individual patient data meta-analysis of randomised trials. J Clin Oncol. 2007; 25:Suppl.8526.abstract.

Ref. 13 Mocellin S, Pasquali S, Rossi CR, Nitti D. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst 2010; 102: 493–501.

Ref. 14 Eggermont AMM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet 2008; 372: 117–26.

Ref. 15 Eggermont AMM, Suciu S, MacKie R, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. Lancet 2005; 366: 1189–96.

Ref. 16 Eggermont AMM, Suciu S, Testori A, et al. Ulceration and stage are predictive of interferon efficacy in melanoma: Results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer 2012; 48: 218–25.

Ref. 17 Eggermont AM, Suciu S, Testori A, Santinami M, Kruit WH, Marsden J, Punt CJ, Salès F, Dummer R, Robert C, Schadendorf D, Patel PM, de Schaetzen G, Spatz A, Keilholz U. Long term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol. 2012 Nov 1;30(31):3810-8.

Ref. 18 Flaherty LE, Moon J, Atkins MB et al. Phase III trial of high-dose interferon alpha-2b versus cisplatin, vinblastin, DTIC, plus IL-2 and interferon in patients with high-risk melanoma (SWOG S0008): an intergroup study of CALGB, COG, ECOG and SWOG. J Clin Oncol 2012;30 Suppl: abstract 8504

Ref. 19 Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Ipilimumab versus placebo after complete resection of stage III melanoma: Initial efficacy and safety results from the EORTC 18071 phase III trial. J Clin Oncol 2014;(suppl):LBA9008

Ref. 20 Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711–23.

Ref. 21 Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364: 2517–26

Ref. 22 Attia P, Phan GQ, Maker AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. J Clin Oncol 2005; 23: 6043–53.

Ref. 23 Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364: 2507–16.

Ref. 24 Hauschild A, Grob J-J, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380: 358–65.

Ref. 25 Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012; 367: 107–14.

Ref. 26 Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012 Nov;367(18):1694-703.

Ref. 27 Lebbé C, Weber JS, Maio M, et al. Long-term survival in patients with metastatic melanoma who received ipilimumab in four phase II trials. J Clin Oncol 2013; 31 suppl; abstr 9053

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Appendix B: Abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
ASCO	American Society of Clinical Oncology
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BMG	Board of Melanoma Group
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Counts
CI	Confidence Interval
CLIND	Complete Lymph Node Dissection
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMFS	Distant Metastases-Free Survival
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FFPE	Formalin Fixed Paraffin Embedded
G-CSF	Granulocyte Colony-Stimulating Factor
HBM	Human Biological Material
HCO3	Bicarbonate
HCT	Hematocrit
HGB	Hemoglobin

HLA	Human Lymphocyte Antigen
HQ	Headquarters
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IB	Investigator brochure
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IHC	Immunohistochemistry
IL-2	interleukin-2
ITP	immune thrombocytopenia
IPI	Ipilimumab
IrAE	Immune-related Adverse Event
IrRC	Immune-related Response Criteria
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	intent-to-treat
IV	Intravenous
K:	Potassium
LDH	Lactate dehydrogenase (enzyme)
LFT	Liver Function Test
Na	Sodium
NCI	National Cancer Institute
NK	Natural Killer
NOEL	No Observable Effect Level
NSCLC	Non-Small Cell Lung Carcinoma
OTC	over-the-counter
ORR	Overall Response Rate

OS	Overall Survival
PD	Pharmacodynamics
PD-L1	Programmed death-ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetics
PPT	Per-protocol treatment
PRFS2	Progression/Recurrence-Free Survival 2
Q2W	Every-2-weeks
Q3W	Every-3-weeks
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
RFS	Recurrence Free Survival
SAE	Serious Adverse Event
SN	Sentinel node
TB	Bacillus Tuberculosis
TNF	Tumor Necrosis Factor
TR	Translational Research
TRAC	Translational Research Advisory Committee
ULN	Upper Limit of Normal
V-Type	Variable- Type

Appendix C: ECOG performance status scale

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix D: EORTC Quality of Life evaluation: guidelines for administration of questionnaires

EORTC Quality of Life evaluation: guidelines for administration of questionnaires

The instructions given below are intended to provide some general guidelines for collecting quality of life (QOL) data in EORTC studies. These instructions apply for all types of questionnaires.

1. Who is the responsible person (RP) for QOL data collection?

In each institution, the principal investigator is the responsible for the local organization of QoL data collection. This can be delegated to a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire(s). This person would also be the intermediate contact point in case of any necessary clarification asked by the EORTC Headquarters.

2. Who should fill out the questionnaire?

In principle it is the patient who has to complete the QOL forms and preferably without help from others. In the case where a patient is too sick to fill out the questionnaire by him/herself or if the patient is not able to complete the questionnaire for such reasons as forgetting his/her glasses, another person could read the questions without making any suggestions and report the answers on the forms. It is not allowed for another person to fill in the questionnaire as if (s)he was the patient (proxy assessment) unless specifically allowed by the protocol.

3. What instructions should be given to the patient?

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for completing the questionnaires.

The patient should be informed that participation in the QOL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes date of birth and today's date (completion date)).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self administered questionnaire that should be completed by the patient him(her)self. The patient can ask for aid in reading or writing but should not let another person provide the answers.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions. The answers will not influence any medical decision making.

- All questions should be answered.
- The patient will be given a questionnaire in the default language(s) of the hospital. If desired, the patient may request another language. The RP will then contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or from other appropriate staff if the RP is unavailable.

4. Where should the patient complete the questionnaire?

The patient should complete the questionnaire at the clinic, and, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take long to complete the questionnaire, but patients should be given the time they need to answer all questions.

5. When should they complete the questionnaire?

The timing of the planned QoL assessments is detailed in the protocol. When a QOL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient is to receive a therapy, the questionnaire should be filled out before administration of the treatment (unless indicated otherwise in the protocol). The questionnaire should not be taken home and/or mailed (unless indicated otherwise in the protocol).

6. Review of the completed questionnaire

After the patient has completed the questionnaire, the person handling the questionnaire should:

- Complete the “Hospital Staff” specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the questionnaire for omissions.

If this is the case:

- Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason and the date of visit should be documented on the corresponding CRF (case report form).

8. Mailing to EORTC Headquarters

A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to complete it.

Thank you very much for your cooperation. If you have any remarks about this leaflet or if you need further information, please contact:

PPD **- EORTC Headquarters:**

Phone: PPD

Fax: PPD

E-mail: PPD

Appendix E: AJCC 2010 for Melanoma

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to define melanoma (Ref. 60, Ref. 61).

TNM 2010 Definitions

Primary tumor (T)

TX: Primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)

T0: No evidence of primary tumor

Tis: Melanoma in situ

T1: Tumor 1.0 mm or less in thickness with or without ulceration

- T1a: Tumor 1.0 mm or less in thickness without ulceration and with mitotic index < $1/mm^2$
- T1b: Tumor 1.0 mm or less in thickness with ulceration or with mitotic index ≥ $1/mm^2$

T2: Tumor more than 1.0 mm but 2.0 mm or less in thickness with or without ulceration

- T2a: Tumor more than 1.0 mm but 2.0 mm or less in thickness with no ulceration
- T2b: Tumor more than 1.0 mm but 2.0 mm or less in thickness with ulceration

T3: Tumor more than 2.0 mm but 4.0 mm or less in thickness with or without ulceration

- T3a: Tumor more than 2.0 mm but 4.0 mm or less in thickness without ulceration
- T3b: Tumor more than 2.0 mm but 4.0 mm or less in thickness with ulceration

T4: Tumor more than 4.0 mm in thickness with or without ulceration

- T4a: Tumor more than 4.0 mm in thickness without ulceration
- T4b: Tumor more than 4.0 mm in thickness with ulceration

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis to one lymph node

- N1a: Clinically occult (microscopic) metastasis
- N1b: Clinically apparent (macroscopic) metastasis

N2: Metastasis to two or three regional nodes or intralymphatic regional metastasis without nodal metastases

- N2a: Clinically occult (microscopic) metastasis
- N2b: Clinically apparent (macroscopic) metastasis
- N2c: In-transit metastasis /satellites or without nodal metastasis

N3: Metastasis in four or more regional nodes, or matted lymph nodes, or in-transit metastasis or satellite(s) with metastatic regional node(s)

[Note: Micrometastases are diagnosed after sentinel lymphnode biopsy. Macrometastases are defined as clinically detectable lymph nodes metastases confirmed pathologically, or when any lymph node metastasis exhibits gross extracapsular extension.]

Distant Metastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

- M1a: Metastasis to skin, subcutaneous tissues, or distant lymph nodes
- M1b: Metastasis to lung
- M1c: Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase

Clinical Staging - AJCC 2010 stage groupings

Clinical staging includes microstaging of the primary melanoma and clinical and/or radiologic evaluation for metastases. By convention, it should be assigned after complete excision of the primary melanoma with clinical assessment for regional and distant metastases (Ref. 60)

Stage 0	Tis, N0, M0
Stage IA	T1a, N0, M0
Stage IB	T1b, N0, M0
	T2a, N0, M0
Stage IIA	T2b, N0, M0
	T3a, N0, M0
Stage IIB	T3b, N0, M0
	T4a, N0, M0
Stage IIC	T4b, N0, M0
Stage III	Any T, N1, M0
	Any T, N2, M0
	Any T, N3, M0
Stage IV	Any T, any N, M1

Pathologic Staging

With the exception of clinical stage 0 or stage IA patients (who have a low risk of lymphatic involvement and do not require pathologic evaluation of their lymph nodes), pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after sentinel node biopsy and, complete lymphadenectomy (Ref. 60)

Stage 0	Tis, N0, M0
Stage IA	T1a, N0, M0
Stage IB	T1b, N0, M0
	T2a, N0, M0
Stage IIA	T2b, N0, M0
	T3a, N0, M0
Stage IIB	T3b, N0, M0
	T4a, N0, M0
Stage IIC	T4b, N0, M0
Stage IIIA	T1-4a, N1a, M0
	T1-4a, N2a, M0
	Tx, N1a, M0
	Tx, N2a, M0
Stage IIIB	T1-4b, N1a, M0
	T1-4b, N2a, M0
	T1-4a, N1b, M0
	T1-4a, N2b, M0
	T1-4a, N2c, M0
	Tx, N1b-2b, M0
	Tx, N2c, M0
Stage IIIC	T1-4b, N1b, M0
	T1-4b, N2b, M0
	T1-4b, N2c, M0
	Any T, N3, M0
Stage IV	Any T, any N, M1

Agreement between pathologists in the histologic diagnosis of melanomas and benign pigmented lesions has been studied and found to be considerably variable. One such study found that there was discordance on the diagnosis of melanoma versus benign lesions in 37 of 140 cases examined by a panel of experienced dermatopathologists (Ref. 62).For the histologic classification of cutaneous melanoma, the highest concordance was attained for Breslow thickness and presence of ulceration, while the agreement was poor for other histologic features such as Clark's level of invasion, presence of regression, and lymphocytic infiltration. In another study, 38% of cases examined by a panel of expert pathologists had two or more discordant interpretations. These studies convincingly show that distinguishing between benign pigmented lesions and early melanoma can be difficult, and even experienced dermatopathologists can have differing opinions. To reduce the possibility of misdiagnosis for an individual patient, a second review by an independent qualified pathologist should be considered (Ref. 63).

The microstage of melanoma is determined on histologic examination by the vertical thickness of the lesion in millimeters (Breslow's classification) and/or the anatomic level of local invasion (Clark's classification). The Breslow thickness is more reproducible and more accurately predicts subsequent behavior of melanoma in lesions larger than 1.5 mm in thickness and should always be reported. Accurate microstaging of the primary tumor requires careful histologic evaluation of the entire specimen by an experienced pathologist. Estimates of prognosis should be modified by sex and anatomic site as well as by clinical and histologic evaluation.

Clark's Classification (Level of Invasion)

Level I: Lesions involving only the epidermis (in situ melanoma); not an invasive lesion.

Level II: Invasion of the papillary dermis but does not reach the papillary-reticular dermal interface.

Level III: Invasion fills and expands the papillary dermis but does not penetrate the reticular dermis.

Level IV: Invasion into the reticular dermis but not into the subcutaneous tissue.

Level V: Invasion through the reticular dermis into the subcutaneous tissue.

Appendix F: Surgical and pathological considerations for melanoma

Surgical considerations

1. Recommendation for management of the primary:

Wide excision with a minimum 1 cm margin surrounding the primary lesion or biopsy scar is recommended for entry onto this protocol. As long as the primary melanoma is completely resected within the margin the resection is acceptable. For lesions whose Breslow's thickness is >2 mm, a 2 cm minimum margin is preferred when anatomically feasible (i.e., for lesions of the trunk and proximal extremities). On other sites narrower margin is preferred to avoid mutilation. For sub-ungual melanoma, a distal interphalangeal amputation with histologically negative margins constitutes an adequate wide excision. The specimen shall be excised to include skin and all subcutaneous tissue down to the muscular fascia. Fascia may be included at the discretion of the operating surgeon. The pathology report should state the surgical margins and adequacy of the resection.

Closure of the defect may be via primary closure, split thickness skin graft, or rotation-flap at the discretion of the surgeon.

2. Sentinel Node Procedure: See guidelines for pathological considerations below. It is mandatory that these guidelines are fully respected in order for the patient to be eligible.

3. Axillary Lymphadenectomy:

For this study a complete axillary lymph node dissection will be performed including nodes at levels I, II and III (level III in case of overt nodal involvement). Axillary node dissection must include at least 10 nodes taken from Levels I and II and the level III nodes dissected for palpable axillary nodes. Minimum of 10 nodes must be pathologically investigated. The boundaries of the dissection should include the axillary vein superiorly beginning at the thoracic outlet and coursing to the latissimus dorsi tendon. The lateral border of the dissection is the anterior edge of the lattisimus dorsi muscle. The posterior boundary is the subscapular muscle. The anterior border of the resection is the pectoralis major group. The inferior boundary of the dissection should be the juncture of the latissimus dorsi and the serratus anterior muscles.

The contents within these boundaries should be completely removed with the exception of the long thoracic nerve and the thorocodorsal nerve which should be identified during the dissection and preserved throughout. As stated, the pectoralis minor muscle may be divided or sacrificed with the specimen at the discretion of the surgeon. Care should be exercised that in the superior part of the dissection, the anterior pectoral nerve is not injured. The preferable approach to the axilla is through a horizontal incision in the line of the skin crease, 3 or 4 cm below the apex of the skin fold of the axilla.

4. Inguinal Lymphadenectomy:

A superficial femoral node dissection should be performed by excising all of the nodes inferior to the inguinal ligament and bounded by the medical border of the sartorius muscle in the lateral border of the adductor magnus muscle. The fatty and lymphatic tissues should be dissected carefully off of the femoral vessels and nerves all the way up to the inguinal

canal and for 3 cm superior to the inguinal ligament. The saphenous vein is resected to ensure complete excision of the lymphnodes. Transposition of the sartorius muscle should be considered (but is not mandatory) to cover the femoral vessels after complete lymphatic excision. Ideally, this area should be entered through a curvilinear incision staring laterally over the inguinal ligament and curving medially and inferiorly ending over the mid-point of the adductor magnus muscle. A superficial femoral node dissection suffices for clinically node negative, but sentinel node positive patients. Minimum of 5 nodes must be pathologically investigated.

5. Deep Inguinal and External Iliac Node Dissection:

Deep Inguinal and External Iliac Node Dissection can be most easily approached by incising the abdominal wall musculature 3 or 4 cm superior to the inquinal ligament. This incision is taken down through the external oblique, internal oblique and transversus muscles and the surgeon at that point stays extraperitoneally as in the approach to the iliac vessels for renal transplantation. With this approach, the external, internal and common iliac arteries are exposed and the lymphatics coursing among the iliac vessels are excised. A full ilio- inguinal (deep) inguinal node dissection is advised in case of overt inguinal node- metastasis and when Cloquet's node is positive.

6. (Modified) Radical Neck Dissection:

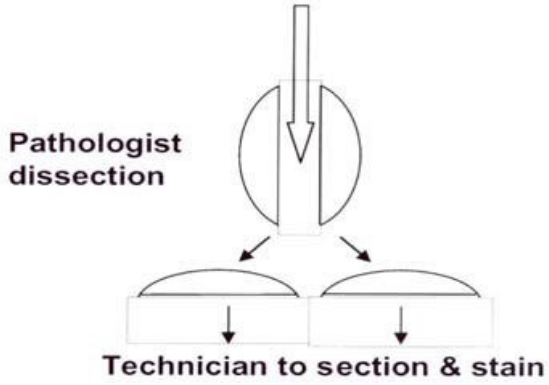
Classic or modified radical neck dissection may be performed for patients with melanoma of the head and neck. Minimum of 15 nodes must be pathologically investigated. As noted above, patients with melanoma located on the ear and anterior scalp and face will require superficial parotidectomy along with a radical neck procedure. The boundaries of the radical neck dissection are inferiorly the clavicle; the mandible, the mastoid and the tail of the parotid gland superiorly; the anterior border of the trapezius muscle posteriorly and the strap muscle of the larynx anteriorly. The sternocleidomastoid muscle may be sacrificed or preserved at the surgeon's discretion. For posterior lesions the radical neck incision must be extended posteriorly or a second incision must be made so that the sub-occipital nodal group can be sampled. For posterior neck dissection, surgical and pathol-ogical exploration of 5 nodes are sufficient to consider the procedure is adequate.

Note: the number of nodes pathologically investigated takes into account nodes removed from the sentinel node dissection and the CLND.

Pathological considerations for Sentinel Lymph Nodes (SLN)

1. Parameters to include in the SLN pathology report are:

- number of sentinel nodes
- number of micro-metastatic sentinel nodes
- for each micro-metastatic sentinel node:
  - topography of the micro-metastasis: capsular, sub-capsular, parenchymatous or sinusal
  - the largest diameter of the tumor cluster



Handling of SLN for melanoma involves bivalving and sectioning the cut surface of both halves

2. Sequence of sectioning and staining in SLN protocol for melanoma

Section 1 (first full section)	H&E
Section 2	S100
Section 3	spare
Section 4	spare
50µ gap (+50µ)	
Section 5	H&E
Section 6	S100
Section 7	spare
Section 8	spare
50µ gap (+100 µ)	
Section 9	H&E
Section 10	S100
Section 11	spare
Section 12	spare
50µ gap (+150µ)	
Section 13	H&E
Section 14	S100
Section 15	spare
Section 16	spare
50µ gap (+200 µ)	
Section 17	H&E
Section 18	S100
Section 19	spare
Section 20	spare

When S100 section reveals micro-metastasis, isolated tumors cells or is doubtful, immunostaining with MELAN-A or HMB45 is performed on the subsequent spared slide.

Appendix G: Guidelines for management of toxicity

The guidelines are based on the guidance provided by Merck.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 23 below. See Events of Clinical Interest Guidance (Appendix H) Document for supportive care guidelines (below), including use of corticosteroids.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT elevation or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hypophysitis	2	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Withhold or permanently discontinue pembrolizumab at the discretion of the investigator or treating physician. If withhold, restart treatment if toxicity resolves to Grade 0-1	Withhold or permanently discontinue pembrolizumab at the discretion of the investigator or treating physician Permanent discontinuation if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3-4	Withhold or permanently discontinue pembrolizumab at the discretion of the investigator or treating physician. If withhold, restart treatment if toxicity	Withhold or permanently discontinue pembrolizumab at the discretion of the investigator or treating physician. Permanent discontinuation if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
		resolves to Grade 0-1	12 weeks.
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted for Grades 2-4	Therapy with pembrolizumab can be continued for Grades 2-4 while thyroid replacement therapy is instituted.
Infusion Reaction (a)	2[a]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Permanent discontinuation if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 or recurrent grade 2	Permanently discontinue	Permanently discontinue
Nephritis and renal dysfunction	2	Toxicity resolves to Grade 0-1	Permanent discontinuation if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Myocarditis	1-2	Toxicity resolves to Grade 0-1	Permanent discontinuation if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	Intolerable/Persistent Grade 2	Toxicity resolves to Grade 0-1	Permanent discontinuation if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: GBS,SOTR, encephalitis If withhold, restart treatment if toxicity resolves to Grade 0-1	Permanently discontinue based on the type of event. Events that require discontinuation include and not limited to: GBS,SOTR, encephalitis If on hold, proceed to permanent discontinuation when toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4 or recurrent grade 3	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM). (a) For patients with infusion reaction Grade 2, if symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated for the next scheduled dose; Refer to Table 24– Infusion Reaction Treatment Guidelines for further management details.			

Table 23: Dose Modification Guidelines for Drug-Related Adverse Events

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

1) Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

2) **Pneumonitis**

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

For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

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

3) Diarrhea/Colitis

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

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

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

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

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

4) Hyperglycemia

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

For T1DM or Grade 3-4 Hyperglycemia

Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5) Hypophysitis

For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

6) Hyperthyroidism or Hypothyroidism

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

Grade 2 hyperthyroidism events (and Grade 3-4 hypothyroidism):

In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

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

Grade 3-4 hyperthyroidism

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

7) Hepatic

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

Treat with IV or oral corticosteroids

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

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

8) Renal Failure or Nephritis

For Grade 2 events, treat with corticosteroids.

For Grade 3-4 events, treat with systemic corticosteroids.

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

9) Infusion reaction

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

below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

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 patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine** Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Patient is permanently discontinued from further trial treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc		

Table 24: Infusion Reaction Treatment Guidelines

Appendix H: Guidelines for Management of Adverse Events (AE) and Events of clinical interest (ECI)

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for pembrolizumab program.

Based on the literature review (Ref. 1 – Ref. 11), and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that must be reported to EORTC within 24 hours (refer Section 16) from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of patient data. Table 25 provides the list of terms and reporting requirements for AEs that must be reported as ECIs for pembrolizumab protocols. Of note, the requirement for reporting of ECIs applies to all arms of pembrolizumab clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab.

Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 25 and reported to EORTC within 24 hours from the time the Investigator/physician is aware of such an occurrence.

Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions

Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Table 25: Events of Clinical Interest

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient.

For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to the Sponsor.

Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event.

Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

ECI reporting guidelines and patient management

ECIs are selected non-serious and serious adverse experiences that must be reported to EORTC within 24 hours regardless of attribution to study treatment. The AEs listed in this chapter and any event that meets the ECI criteria (as noted) in Table 25 or in the respective protocol (event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified).

- **PNEUMONITIS**

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to EORTC within 24 hours of the event:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics. If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2	Report as ECI Hold pembrolizumab. Consider pulmonary consultation with bronchoscopy and biopsy/BAL. Consider ID consult Conduct an in person evaluation approximately twice per week Consider frequent Chest X-ray as part of monitoring

CTCAE Grade	Course of Action
	Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Add prophylactic antibiotics for opportunistic infections. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.
Grade 3 and 4	Report as ECI Discontinue pembrolizumab. Hospitalize patient Bronchoscopy with biopsy and/or BAL is recommended. Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed Add prophylactic antibiotics for opportunistic infections.

Table 26: Pneumonitis

- **COLITIS**

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to EORTC within 24 hours of the event:

- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic

- Gastrointestinal perforation
- Intestinal obstruction
- Necrotizing colitis
- Diarrhea

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

CTCAE Grade	Course of Action
Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool)	Report as ECI Hold pembrolizumab. Symptomatic Treatment For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus, Consider GI consultation and endoscopy to confirm or rule out colitis Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. If symptoms worsen or persist > 3 days treat as Grade 3

CTCAE Grade	Course of Action
Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persist for greater than 3 days)	Report as ECI Hold pembrolizumab. Rule out bowel perforation. Imaging with plain films or CT can be useful. Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy. Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.
Grade 4	Report as ECI Permanently discontinue pembrolizumab. Manage as per Grade 3.

Table 27: Colitis

- **ENDOCRINE**

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to EORTC within 24 hours of the event:

- Adrenal insufficiency
- Hyperthyroidism

- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Thyroid disorder
- Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2-4	Report as ECI if appropriate Hold pembrolizumab Rule out infection and sepsis with appropriate cultures and imaging Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis Consultation with an endocrinologist may be considered.

Table 28: Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

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

CTCAE Grade	Course of Action
Grade 2 event hyperthyroidism Grade 3-4 hypothyroidism	Report as ECI if appropriate (see Table 25) Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted. In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy. In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care. Consultation with an endocrinologist may be considered.
Grade 3 hyperthyroidism	Report as ECI Hold pembrolizumab. Rule out infection and sepsis with appropriate cultures and imaging. Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Grade 4	Report as ECI Discontinue pembrolizumab. Manage as per Grade 3

Table 29: Hyperthyroidism and Hypothyroidism

♦ **HEMATOLOGIC**

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to EORTC within 24 hours of the event:

- ♦ Autoimmune hemolytic anemia
- ♦ Aplastic anemia
- ♦ Disseminated Intravascular Coagulation (DIC)
- ♦ Haemolytic Uraemic Syndrome (HUS)
- ♦ Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
- ♦ Thrombotic Thrombocytopenic Purpura (TTP)
- ♦ Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2	Report as ECI Hold pembrolizumab Prednisone 1-2 mg/kg daily may be indicated Consider Hematology consultation. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Grade 3	Report as ECI Hematology consultation. Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance. Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

CTCAE Grade	Course of Action
Grade 4	Report as ECI Hematology consultation Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies. Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

Table 30: Hematologic ECIs

- **HEPATIC**

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to EORTC within 24 hours of the event:

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

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

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

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

CTCAE Grade	Course of Action
Grade 2	Report as ECI Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN. Monitor liver function tests more frequently until returned to baseline values (consider weekly). Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

CTCAE Grade	Course of Action
Grade 3	Report as ECI Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN. Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks. If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Grade 4	Report as ECI Permanently discontinue pembrolizumab Manage patient as per Grade 3 above

Table 31: Hepatic adverse ECIs

♦ **NEUROLOGIC**

The following AE terms, regardless of grade, are considered ECIs and should be reported to EORTC within 24 hours of the event:

- ♦ Autoimmune neuropathy
- ♦ Demyelinating polyneuropathy
- ♦ Guillain-Barre syndrome
- ♦ Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2	Report as ECI Moderate (Grade 2) – consider withholding pembrolizumab. Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate Consider Neurology consultation. Consider biopsy for confirmation of diagnosis. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Grade 3 and 4	Report as ECI Discontinue pembrolizumab Obtain neurology consultation. Consider biopsy for confirmation of diagnosis Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines
When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	

Table 32: Neurologic ECIs

♦ **OCULAR**

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to EORTC within 24 hours of the event:

- Uveitis
- Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2	Evaluation by an ophthalmologist is strongly recommended. Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.
Grade 3	Evaluation by an ophthalmologist is strongly recommended Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance. Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Grade 4	Evaluation by an ophthalmologist is strongly recommended Permanently discontinue pembrolizumab. Treat with corticosteroids as per Grade 3 above

Table 33: Ocular ECIs

- **RENAL**

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure

- Renal failure acute
- Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2	Hold pembrolizumab Treatment with prednisone 1-2 mg/kg p.o. daily. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Grade 3-4	Discontinue pembrolizumab Renal consultation with consideration of ultrasound and/or biopsy as appropriate Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.
When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	

Table 34: Renal ECIs

- **SKIN**

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR

- rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs

The following AEs should always be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:

- Dermatitis exfoliative
- Erythema multiforme
- Steven's Johnson syndrome
- Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2	Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl). Treatment with oral steroids is at physician's discretion for Grade 2 events.
Grade 3	Hold pembrolizumab. Consider Dermatology Consultation and biopsy for confirmation of diagnosis. Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Grade 4	Permanently discontinue pembrolizumab. Dermatology consultation and consideration of biopsy and clinical dermatology photograph. Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Table 35: Skin ECIs

♦ IMMEDIATE EVALUATION FOR POTENTIAL SKIN ECIs

A. Photographs:

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

- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.
- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the patient's study records.
- The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:

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

C. Presentation of the Event:

Collect information on clinical presentation and potential contributing factors using the questions in Appendix J (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:

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

E. Focused Skin Examination:

Perform a focused skin examination using the questions in Appendix K (Focused Skin Examination) as a guide. Information should be summarized and entered on the eCRF.

F. Dermatology Consult

Refer the patient to a dermatologist as soon as possible.

- For a "severe rash", the patient must be seen within 1-2 days of reporting the event.
- For clinically significant rash, the patient should be seen within 3-5 days.

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

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

♦ **OTHER**

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- ♦ Myocarditis
- ♦ Pericarditis
- ♦ Pancreatitis
- ♦ Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

CTCAE Grade	Course of Action
Grade 2 or Grade 1 that do not improve with symptomatic treatment	Withhold pembrolizumab. Systemic corticosteroids may be indicated. Consider biopsy for confirmation of diagnosis. If pembrolizumab held and corticosteroid required, manage as per grade 3 below.
Grade 3	Hold pembrolizumab Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol.
Grade 4	Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. Discontinue pembrolizumab

Table 36: Other ECIs

♦ INFUSION REACTIONS

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- ♦ Allergic reaction
- ♦ Anaphylaxis
- ♦ Cytokine release syndrome
- ♦ Serum sickness
- ♦ Infusion reactions
- ♦ Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Patient is permanently discontinued from further study treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room 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		

Table 37: Infusion reactions ECIs

- **FOLLOW UP TO RESOLUTION**

Patients should be followed to resolution. The eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded.

Narrative information requested:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery

- Follow-up to the clinical course

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

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Appendix I: Past Medical History Related to Dermatologic Event

Past Medical History:

Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc):
_____

_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____

_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____

_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

Appendix J: Presentation of the Dermatologic Event

Presentation of the event:

Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug? _____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. Molluscum Contagiosum)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No

ii. Signs of hypotension? □ Yes □ No

iii. Signs of dyspnea? □ Yes □ No

iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____

_____

13. Is the rash pruritic (itchy)? □ Yes □ No

Appendix K: Focused Skin Examination

Focused Skin Examination:

Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description

Color: _____

General description:

_____

_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____

_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____

_____

Any associated signs on physical examination?

_____

Appendix L: 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."

VI. Letter to Patients

At the close of the trial after unblinding, a letter is to be sent by the investigator to those subjects who received placebos to provide the following advice:

"You have participated in a trial conducted by the Sponsor. This is to advise you that you were among those who received placebo. You may also have received the active drug Pembrolizumab."

Appendix M: EQ-5D-3L – Health Questionnaire

Health Questionnaire

(English version for the UK)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

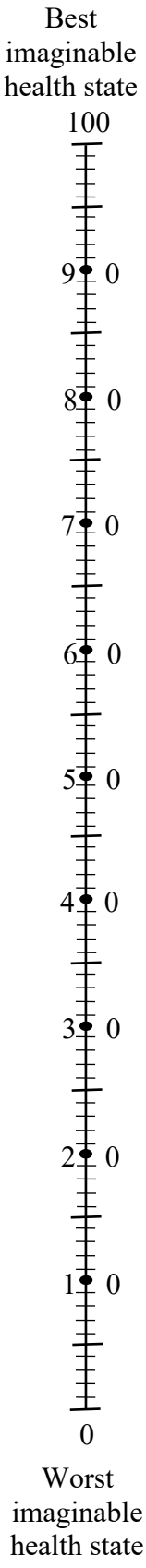
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix N: Recommendations for Contraception in United Kingdom, Portugal, Scandinavian countries and Other Applicable Countries

It is unknown whether pembrolizumab has adverse effects on a fetus in utero or on the composition of sperm. Therefore, non-pregnant, non-breast-feeding women may only be enrolled if they are willing to follow the Clinical Trial Facilitation Group (CTFG) guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal[1] (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active[2] for the duration of the study.

(1) and (2) Refer to Portugal section below

Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence[3]

(3) Refer to Portugal section below

Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 16.8 Reporting of

Pregnancy. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Monthly[4] pregnancy testing is recommended per local standards if applicable.

(4) Refer to Portugal section below

Specific guidelines for Portugal

1. For Portugal postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

2. For Portugal the absence of heterosexual activity refers to sexual abstinence.

3. For Portugal, sexual abstinence (relative to heterosexual activity) can be used as the sole method of contraception only when it is consistently employed as the subject's preferred and usual lifestyle, and if considered acceptable by local regulatory agencies and ethical committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

4. For Portugal, pregnancy testing should be performed at monthly intervals.

Appendix O: Guidelines for RECIST 1.1

1. Criteria of evaluation

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST (Ref. 69) document also available at http://www.eortc.be/RECIST.

1.1 Measurability of tumor lesions at baseline

1.1.1 Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- **Target Lesions**. When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 3 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a *short* axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 3 is to be calculated and recorded.

- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

1.1.2 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray**. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions > 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI**. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.
- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

- **Tumor Markers**. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

1.1.3 Tumor response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment. If on further documentation PD is confirmed, the earlier date must be used. **If this is not the case, so the subsequent disease evaluation does not confirm the PD (i.e. the first PD rather corresponds to a tumor flare reaction), patient should not be considered as having PD, and treatment should be continued.**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 12 wks. from previous assessment
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, all tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration*". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

Table 38: Integration of Target, non-Target and New lesions into response assessment:

1.1.3.1 Frequency of tumor re-evaluation

See Chapter 6.3.6.

1.1.3.2 Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met, unless this corresponds to a tumor flare reaction.

1.1.4 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation.

Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

1.1.5 Response duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

1.1.6 Stable disease duration

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met.

EORTC protocol 1325-MG - Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double- blind Phase 3 trial of the EORTC Melanoma Group

Amendment MK3475-054-03

The changes in this new amendment are:

- To allow radiotherapy as adjuvant therapy treatment after 1st recurrence and prior to entry in Part 2. This has been introduced as, in some participating countries, radiotherapy is part of standard of care after recurrence. It has been implemented in the following sections :
  - 4.2 Part 2 : after the first recurrence : changes to allow radiotherapy before entering Part 2 "Surgery, biopsy and/or radiotherapy (palliative or adjuvant) are allowed prior to Part 2. Radiotherapy has to be completed prior to first dose and complete wound healing is required prior to first dose"
  - 4.3 Unblinding data : changes in Figure 3 Trial design to reflect changes in treatment duration and radiotherapy allowed before Part 2
  - 5.4.2 Part 2 After the first recurrence : changes to allow radiotherapy before Part 2
  - 5.6.1 Prohibited medications, therapies and procedures : changes to allow radiotherapy

- Duration of treatment in Part 2 will be flexible for patients with local recurrence and treatment may stop after 1 year (left to investigator's discretion). It has been implemented in the following sections:
  - Summary : Modification of the treatment duration : Treatment in Part 2 will be administered up to 1 year (local recurrence) or 2 years treatment period unless occurrence of a withdrawal criterion (see Section 5.4.2.4). For patients with local recurrence, the treatment may stop at 1 year at the discretion of the investigator.
  - 4.3 Unblinding data : changes in Figure 3 Trial design to reflect changes in treatment duration and radiotherapy allowed before Part 2
  - 5.4 Treatment schedule : changes in Figure 4 Treatment schedule : to reflect changes in treatment duration
  - 5.4.2.3 Treatment duration for pembrolizumab : changes of treatment duration
  - 5.4.2.4 Withdrawal criteria for Part 2 treatment : changes of treatment duration
  - 6.3.6.2 Evaluations for patients receiving pembrolizumab: changes of treatment duration
  - 6.3.8.1 For patients who discontinued Part 2 due to progression or recurrence or completion of treatment
  - 6.4.2.1 Evaluations during cross over or rechallenge with pembrolizumab : changes of treatment duration

- Frequency of imaging work up in Part 2 will be every 12 weeks instead of 6 weeks
  - 6.3.6.2 Evaluations for patients receiving pembrolizumab
  - 6.4.2.1 Evaluations during cross over or re-challenge with pembrolizumab

- Clarification that patients in follow up will continue imaging assessments as indicated:
  - 6.4.1.2 Follow up evaluation for Part 1 – footnote 3
  - 6.4.2.3 Follow up evaluation for patients who discontinue Part 2 – footnote 3

- Other minor clarifications:
  - Updated CRO representative's contact information
  - Summary, Section 3.3 Enrollment and Randomization chapter and Section 4.2 Part 2 : after the first recurrence (cross-over or re-challenge treatment): Clarification about the creatinine levels allowed for entering Part 2
  - 6.3.1 Part 1 : adjuvant therapy : changes of allowed window for tests to be performed every 12 weeks
  - 6.3.2. Translational research : clarification that baseline TR samples can be collected after randomization but before treatment start