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Intergroup Study (EORTC-1416-LCG)

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A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (PEARLS) KEYNOTE-091

Coordinating Group: EORTC Lung Cancer Group
Collaborative Groups: ETOP

EORTC Study Coordinator: PPD
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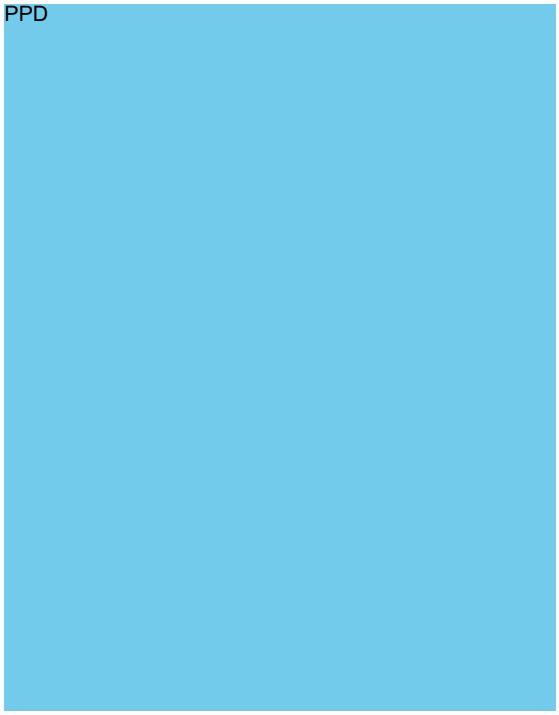

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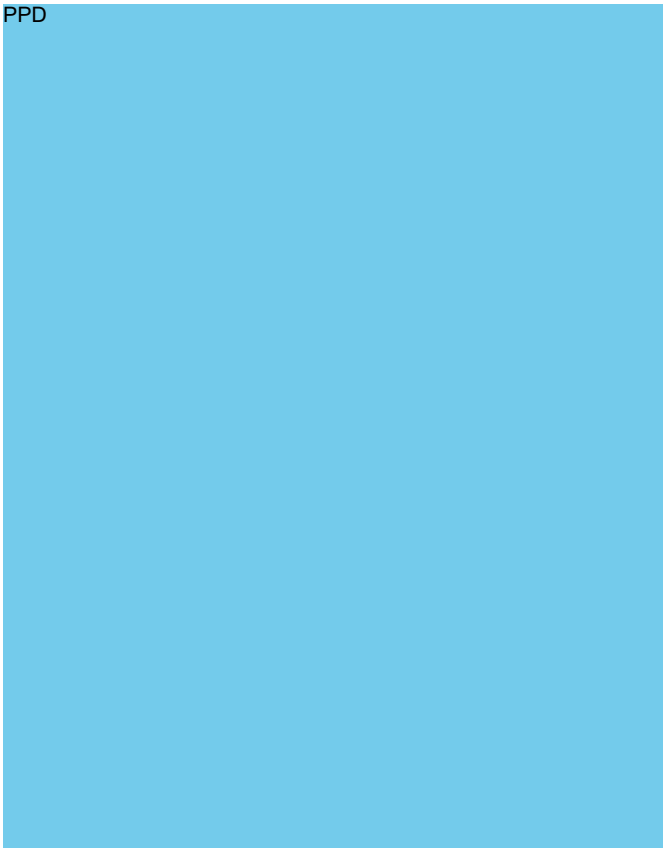

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I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance 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 Chapter 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

_____	_____	_____
Investigator's full name (in capitals)	(Signature)	(Date)

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Protocol summary

Title of the Study	A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (PEARLS).
Objective(s)	**Primary/dual-primary.** To prospectively investigate whether adjuvant treatment with pembrolizumab after completion of radical surgery (lobectomy/pneumonectomy) with or without standard adjuvant chemotherapy for stage IB ($T \geq 4$ cm) -II-IIIA NSCLC patients improves Disease Free Survival (DFS), as assessed locally by the investigator, compared to placebo in the PD-L1 strong positive subgroup (TPS≥50%) or overall population. Note: TNM stage (according to the 7th edition of the TNM classification for lung cancer) **Secondaries.** ♦ To prospectively compare DFS as assessed by the investigator in the PD-L1 positive population (TPS≥1%); ♦ To prospectively determine and compare OS in the PD-L1 strong positive and overall population; ♦ To prospectively determine and compare OS in the PD-L1 positive population; ♦ To prospectively determine and evaluate the Lung Cancer Specific Survival (LCSS) in the whole population irrespective of PD-L1 status; ♦ To prospectively assess the safety of pembrolizumab after radical surgery followed by standard adjuvant chemotherapy. **Exploratory.** ♦ To assess outcome according to stratification factors and other prognostic and predictive markers for NSCLC; ♦ To evaluate these treatments in the elderly (age ≥70 years old); ♦ To prospectively study the influence of dose and duration of adjuvant chemotherapy on outcome; ♦ To prospectively assess genetic alterations and biomarkers of immunological pathways with outcome; ♦ To prospectively assess DNA mutational burden and nanostring RNA analysis with outcome; ♦ To prospectively assess EQ-5D health state profiles at pre-specified time points;

Endpoints	♦ To prospectively assess Health-Related Quality of Life (HRQOL); ♦ To evaluate the pharmacokinetics (PK) of pembrolizumab in this patient population to determine the pembrolizumab exposure-response relationships for measures of effectiveness, toxicity and pharmacodynamic biomarkers in the study population; ♦ To evaluate the development of anti-drug antibodies (ADA) against pembrolizumab (immunogenicity evaluation); ♦ To assess and describe the quality assurance for surgery. **Primary/dual-primary endpoints.** ♦ DFS in the PD-L1 strong positive subgroup; ♦ DFS in the overall population. **Secondary endpoints.** ♦ DFS in the PD-L1 positive population; ♦ OS in the overall population; ♦ OS in the PD-L1 strong positive subgroup; ♦ OS in the PD-L1 positive population; ♦ LCSS in the overall population; ♦ Toxicity according to CTCAE version 4.03. **Exploratory endpoints.** ♦ Health-Related Quality of Life (HRQOL); ♦ Pharmacokinetics (PK) of pembrolizumab; ♦ ADA serum titers against pembrolizumab; ♦ Quality assurance for surgery; ♦ Exploratory assessment of predictive biomarkers and immune dynamics (Translational research).

Methodology	This is an international, triple-blinded, placebo-controlled, randomized phase III trial to compare pembrolizumab versus placebo after complete resection of stage IB (T ≥ 4 cm), II and IIIA NSCLC, followed by standard adjuvant chemotherapy, where appropriate as per relevant local guidelines, in patients who have signed the informed consent. Note: TNM stage (according to the 7th edition of the TNM classification for lung cancer) Enrollment will be a multi-step process. A total of 1180 eligible patients will be randomized at 1:1 ratio into two triple blinded, treatment arms (approximately 590 patients each): ♦ Patients in the experimental arm will receive pembrolizumab (see Sections 5.2 and 5.4); ♦ Patients in the control arm will receive placebo (see Sections 5.1 and 5.4). Patients not receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date. Participants who receive adjuvant chemotherapy must begin adjuvant chemotherapy within 12 weeks of the surgery date. Patients receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo at least 3 weeks but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle). Randomization will be performed centrally (see Chapter 15) and will be stratified for the following factors: ♦ Stage (IB vs II vs IIIA); ♦ Adjuvant chemotherapy (no adjuvant chemotherapy versus adjuvant chemotherapy); ♦ PD-L1 (3 groups: negative (TPS=0%) versus weak positive (TPS=1-49%) versus strong positive (TPS≥50%); ♦ Region (Western Europe versus Eastern Europe versus Rest of the world versus Asia).

Number of patients Number planned (Statistical design) Number analyzed	A sample size of 1180 randomized patients is planned and the primary analysis is based on intent to treat (all 1180 patients). CCI [redacted] The study is designed with primary/dual-primary endpoints: DFS in the whole population and DFS in the PD-L1 strong positive sub-populations. Assumptions and testing strategy are given below. ♦ Overall, an improvement of 14 months in median DFS (from 42 months to 56 months) or equivalent to HR = 0.75 is aimed for the whole population. CCI [redacted] ♦ The HRs for OS between the experimental and control arms are 0.6, 0.7 and 0.765, for PD-L1 strong positive, PD-L1 positve and the whole population, respectively. ♦ CCI [redacted] he enrollment duration is 52 months with the accrual rates provided in Table 7 below. ♦ The yearly drop-out rate is 2.5% and 1% for DFS and OS, respectively. Table 7 – Enrollment Pattern **Period** / **Starting at time** / **Calendar Time** / **Accrual Rate** 1 / 0 / January 2016 / 8.375 2 / 8 / September 2016 / 18 3 / 26 / March 2018 / 34.24 4 / 47 / December 2019 / 13.992 ♦ The family-wise error rate (Type I error) for DFS and OS hypotheses is strongly controlled at 2.5%, one-sided. The study uses the graphical method of Maurer and Bretz [Ref. 75] to provide strong multiplicity control for multiple hypotheses as well as interim efficacy analyses. See Figure 3 for an overview of the multiplicity strategy. ♦ CCI [redacted] analysis, OS analysis will be performed as well. There are three additional analyses for OS alone after DFS FA. The schedule and characteristics of analyses are given in Table 8 and Table 9 in Section 8.1.1.

	♦ A Hwang-Shih-DeCani (HSD) spending function with gamma = -4 is used to establish the boundary (nominal alpha) in interim and final analysis of DFS and OS for the test of each population. The threshold alphas and HRs for each analysis can be found in Table 8 and Table 9 in Section 8.1.1. ♦ The timing of interim analysis 1 and 2 will be determined by the number of DFS events in the PD-L1 strong positive population, and the final analysis for DFS will be conducted when target DFS event numbers are reached in the whole population as well as the PD-L1 strong positive subgroup. Approximately 1180 participants will be randomized in a 1:1 ratio into the experimental arm and the control arm. For DFS, based on a target number of 551 events at FA, the study has ~86% power at alpha=1.25% (one-sided) and ~92% power at alpha=2.5% (one-sided) for the whole population. It is expected that there will be approximately 334 participants of PD-L1 strong positive in the study to achieve ~90% power at final analysis of DFS at alpha=1.25% (one-sided) and ~94% power at alpha=2.5% (one-sided). If either of the tests for the primary endpoints is significant, then the study can be declared successful in the respective population.
Diagnosis and main criteria for inclusion	Patient enrollment will follow a three-step procedure as illustrated in Chapter 4 (step 1 registration, step 2 central confirmation of PD-L1 status, step 3 randomization). Patients must meet all of the criteria described in Sections 3.1, 3.2 and 3.3 to be eligible for randomization in step 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. For patients that accept to participate in the translational research, we recommend the informed consent for translational research be signed before registration step 1;** ♦ Pathological diagnosis of NSCLC confirmed at surgery, any histology is eligible; ♦ Confirmed UICC v7 stage IB with T ≥ 4 cm, II-IIIA NSCLC after complete surgical resection (lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy) as documented in the pathology report; (Note: TNM stage according to the 7th edition of the TNM classification for lung cancer) ♦ Resection margins proved microscopically free (R0); Resection margins are evaluated at the bronchial, venous and

	arterial stumps, peribronchial soft tissue, any peripheral margin near the tumor or of additionally resected tissue; ♦ A systematic complete mediastinal lymph node dissection or a lobe-specific mediastinal lymph node dissection (Appendix K) is recommended. At a minimum, the pathology and/or operative report must include the examination of at least two different mediastinal lymph node (N2) levels, one of which is the subcarinal (level 7) and the second of which is lobe-specific; ♦ In the uncommon clinical situation where the surgeon thoroughly examines a particular mediastinal lymph node level and does not find any lymph nodes, that mediasintal lymph node level may be counted among the minimum two required levels. However, the surgeon **must** clearly document in the operative report or in a separate written statement that the lymph node level was explored and **no** lymph nodes were present. Normal appearing lymph nodes, if present, must be biopsied or/removed;No extracapsular extension of tumor in resected mediastinal (N2) lymph nodes. Extracapsular tumor extension is permitted in resected N1 lymph nodes; ♦ The highest mediastinal node removed can be positive for malignancy; ♦ Carcinoma in situ can be present at bronchial margin; ♦ Patients with two synchronous primary non-small cell lung cancers are excluded from the study; ♦ Availability of tumor sample obtained at surgical resection for PD-L1 Immunohistochemistry (IHC) expression assessment. Patients must submit the tumor sample during screening for PD-L1 IHC expression testing at a central pathology laboratory. Patients will be eligible to participate regardless of the level of PD-L1 status, however tissue must be considered satisfactory for characterization of PD-L1 status. Patients whose samples are inadequate for PD-L1 determination will not be randomized; ♦ Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides must be freshly cut and submitted to the central testing laboratory; ♦ At least 18 years; ♦ **2) Central confirmation of PD-L1 status - step 2** This central confirmation through EORTC is required for enrolling the patient in step 3.

	3) Randomization - step 3 (ORTA step 2) ♦ **Before patient randomization, written informed consent ('Main Study') for participation in the study must be given according to ICH/GCP, and national/local regulations**; ♦ No evidence of disease (NED) at clinical examination and baseline radiological assessment as documented by contrast enhanced chest/upper abdomen CT scan, brain CT/MRI and clinical examination within 12 weeks prior to the randomization date; ♦ Adjuvant chemotherapy is not mandatory but considered for patients with stage IB ($T \geq 4$ cm) and strongly recommended for stage II and IIIA, and will be administered according to national and local guidelines. Patients who received more than 4 cycles of adjuvant therapy are not eligible; ♦ Patients not receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date. ♦ Participants who receive adjuvant chemotherapy must begin adjuvant chemotherapy within 12 weeks of the surgery date. Patients receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo at least 3 weeks but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle). ♦ ECOG Performance status 0-1; ♦ Adequate organ function performed within 10 days of treatment initiation; ♦ No prior or planned neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy is allowed; ♦ No prior treatment with an anti-PD-1, anti-PD-L1/2, anti-CD137, CTLA-4 modulators or any other immune-modulating agents ; patients receiving live vaccine within 30 days prior to the first infusion of study treatment are not eligible; ♦ No current participation in a interventional clinical trial or treatment with an investigational agent or use of an investigational device within 4 weeks of the first infusion of study treatment; ♦ No known history of Human Immunodeficiency Virus (HIV) (known HIV 1/2 antibodies positive). No known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay;

	♦ No chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 3 days prior to the first infusion of trial treatment: ♦ Corticosteroid use on study for management of ECIs (pembrolizumab Event of Clinical Interest), as premedication for the administration of chemotherapies, and/or a premedication for IV contrast allergies/reactions is allowed; ♦ Daily prednisone at doses of 5-7.5 mg is allowed as an example of replacement therapy. Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy; ♦ No history of interstitial lung disease (ILD) OR a history of (non-infectious) pneumonitis that required oral or IV steroids (other than COPD exacerbation) or current pneumonitis; ♦ No active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Any replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. Patients with hyperthyroidism or hypothyroidism but that are stable on hormone replacement are also allowed; ♦ No history of a hematologic or primary solid tumor malignancy, unless in remission for at least 5 years. A pT1-2 prostatic cancer Gleason score < 6, superficial bladder cancer, non melanomatous skin cancer or carcinoma in situ of the cervix is eligible; **Note**: prior radiotherapy for another malignancy (breast cancer/lymphoma/germ cell tumors, etc.) is not an exclusion criterion, the same applies for prior anti-cancer systemic chemotherapy. ♦ No previous allogeneic tissue/solid organ transplant; ♦ No active infection requiring therapy; ♦ No surgery or chemotherapy related toxicity (non-hematological, toxicity resolved to grade 1 (see Appendix D), with the exception of alopecia, fatigue, neuropathy and lack of appetite /nausea); ♦ Female patients with childbearing potential must have a negative urine or serum pregnancy test at screening (within 72 hours of first infusion of study medication). If the urine test cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as (by other than medical reasons); ♦ ≥45 years of age and has not had menses for greater than 1 year;

	♦ Amenorrheic for > 2 years without a hysterectomy and oophorectomy and an FSH value in the postmenopausal range upon pretrial (screening) evaluation; ♦ Whose status is post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last infusion of study treatment (see Appendix L). Information must be captured appropriately within the site's source documents; ♦ If of childbearing potential, female patients must be willing to use two adequate barrier methods throughout the study, starting with the screening visit up to 120 days after last infusion of chemotherapeutic and investigational agents as specified in the protocol; Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Please refer to Appendix M for recommendation based on Clinical Trial Facilitation Group guidelines for sites and countries where applicable (e.g. United Kingdom, Norway, Sweden, Portugal, etc.); ♦ Male patients with a female partner(s) of child-bearing potential must agree to use two adequate barrier methods throughout the trial starting with the screening visit through 120 days after the last infusion of study treatment is received (see Appendix L). Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner; Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Please refer to Appendix M for recommendation 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 must discontinue nursing prior to the first infusion of study treatment and until 120 days after the last study treatment; ♦ Absence of severe comorbidities that in the opinion of the Investigator might hamper the participation to the study and/or the treatment administration;

	After the enrollment step in ORTA, patients will be automatically randomized in the Interactive Voice Response System (IVRS). **Important note: An additional +2 day window is allowed for randomization. All eligibility criteria must be adhered to.**
Treatment Test product, dose, duration and mode of administration	Pembrolizumab at a dose of 200 mg, administered by IV infusion, every 3 weeks, for a total of 18 infusions, approximately one year. Placebo administered by IV infusion, every 3 weeks, for a total of 18 infusions, approximately one year.
Criteria for evaluation Efficacy	**Disease free survival** (DFS) Definition of date of disease recurrence is given in Section 7.1.1.3. Recurrence of disease can be a loco-regional recurrence, a distant (metastatic) recurrence or a second primary. NSCLC and second malignancies will be considered to be events. DFS is calculated as the time from randomization to either the date of disease progression or the date of death (whatever the cause). The date of first documented disease recurrence (if applicable) will be used as the date of event. Patients alive with no evidence of disease recurrence at the time of their last visit are censored at the time of the last examination. **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. **Lung Cancer Specific Survival** (LCSS) is calculated as the time from randomization to the date of death (due to lung cancer specifically). The follow-up of patients still alive will be censored at the moment of last visit/contact. Patients who die but not due to lung cancer are censored at the time of death.

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.
Statistical methods	**Efficacy endpoints** The analyses of the primary and secondary endpoints (DFS, OS and LCSS) will be performed on all randomized patients according to the intention to treat principle. **Estimates and confidence intervals** Estimates of the median DFS, OS and LCSS will be obtained by the Kaplan Meier technique. The 95% confidence interval (CI) for the median will be calculated using the reflected CI method. Estimates of the event-free rate at a fixed time point will be obtained using the Kaplan Meier technique and 95% CI will be calculated by the Greenwood's formula for standard deviation. Estimates of hazard ratios and their 95% CI will be obtained by Cox regression. Kaplan Meier Curves will be drawn for both the experimental and control arms on the same plot. **Inference** The DFS and OS will be analyzed by a Cox Proportional Hazard Regression with treatment adjusted by the following covariates: stratification factors including stage, PD-L1 IHC expression, adjuvant chemo and regions, and additional factors including histology and smoking status. Permutation test [Ref. 74] will be used as a primary test for DFS to compare the experimental versus the control arm. The Wald test without permutation of allocation sequence will be used as a supportive analysis for DFS, but as a primary test for OS. The hazard ratios and corresponding 95% CIs will be estimated using the multivariate Cox regression model stated above (using Efron's tie-handling method). A sensitivity analysis will include sex and age as additional adjustment factors in the Cox regression model. A logrank test with no adjustment factors to compare the two arms will also be performed as a sensitivity analysis. Analysis of LCSS will be based on log-rank test, Cox regression and competing risks approaches. **Toxicity** Analysis for toxicity is based on the safety population. The worst grade of toxicity/adverse events observed over the whole treatment period according to CTCAE version 4.03 will be displayed. In the primary analysis, no formal statistical analysis will be performed to compare toxicity in both arms.

	Health-Related Quality of Life The analyses for Quality of life are defined in Section 10.5. **Proportion of PD-L1 + status** Proportion of PD-L1 status: negative (no staining), weak positive (tumor proportion score (TPS) 1-49%) and strong positive (TPS ≥ 50%) will be checked and reported when approximately 100 patients accrued. In case there is any large departure from current assumption of PD-L1 status, appropriate statistical adjustment will be considered.
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 6.2.4, 6.6, 6.8.2. **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	**The exploratory parameters in this study will be refined according to the current knowledge in the field during trial advancement and at the time of trial completion.** A preliminary proposal of the main objectives of the TR project could be at least (i.e. not limited to) to define: ♦ Biomarker assessment including but not limited to PD-L1, PD-L2 and other immune biomarkers (immune platform) performed on tumor tissue and blood samples respectively; ♦ Intratumoral heterogeneity of PD-L1 status; ♦ Comparison of PD-L1 status between the primary tumor and at relapse (optional rebiopsy); ♦ Exploration of other markers of T cell activation in the PDL1 positive and negative patients; ♦ DNA mutational burden and nanostring RNA analysis.
Health Related Quality of Life	Health Related Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3, EORTC QLQ-LC13 and EQ-5D.

Trial organization

- This trial is an Intergroup Trial, jointly conducted with ETOP in different countries of European Union and third countries;
- Merck Sharp & Dohme LLC (hereafter referred to as the Sponsor or MSD) is the Sponsor in all participating countries;
- The EORTC is the coordinating group in this trial and therefore will centrally manage trial design and activation, data collection and quality control of data, statistical analysis and publication;
- This trial is fully supported by the industry.

1 Background and introduction

1.1 Early stage Non Small Cell Lung Cancer

Lung Cancer is the leading cause of cancer-related death world-wide; in 2012, 313,000 new cases have been estimated in Europe and 1,825,000 worldwide with 268,000 and 1,590,000 deaths respectively [Ref. 1, Ref. 2].

Non Small Cell Lung Cancer (NSCLC) accounts for 80-85% of all lung cancers, about 20% of cases being diagnosed at an early stage when the disease is still curable by surgery.

The most common histological subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma (SqCC), and large-cell carcinoma (LCC). Immunohistochemistry is often helpful in distinguishing between these subtypes; SqCCs is usually TTF-1-negative and p63-positive, whereas adenocarcinomas are often TTF-1-positive. This differentiation can dictate treatment management in the advanced stage but not for surgery or adjuvant chemotherapy [Ref. 3].

Age, performance status (PS) and stage are the main prognostic factors in early stage NSCLC. Gene sequencing studies in early-stage NSCLC have reported prognostic signatures, but no signatures have been prospectively validated in independent studies. The use of biomarkers predicting adjuvant chemotherapy efficacy has recently been evaluated in the LACE bio group without strong recommendations for further studies [Ref. 4].

Surgical resection is the standard treatment for operable patients with resectable stage I to IIIA [Ref. 5, Ref. 6].

The surgical procedure used depends on the extent of the disease and on the cardiopulmonary reserve of the patient. Lobectomy or pneumonectomy with lymphadenectomy are the main options according to the location and size of the tumor, age, performance status (PS), general comorbidities and lung function of the patient [Ref. 7]. Video-assisted thoracoscopic surgery (VATS) may be an alternative to thoracotomy for patients undergoing lobectomy [Ref. 8]. This is a minimally invasive approach that decreases surgical morbidity, including perioperative pain, and is particularly useful for those with significant medical comorbidities [Ref. 9]. Although the efficacy of VATS compared to conventional surgical techniques has not been definitively established, several large case series support the safety and efficacy of this technique for patients with stage I NSCLC [Ref. 10, Ref. 11, Ref. 12].

In 2006, the European Society of Thoracic Surgeons guidelines recommended systematic lymph node dissection in all cases to ensure complete resection [Ref. 13]. The optimal extent of lymph node resection is uncertain: a meta-analysis concluded that systematic mediastinal nodal dissection (levels 4, 7, and 10 for right sided lesions, and levels 5 or 6 and 7 for left sided lesions) was associated with a small to moderate improvement in survival compared with lymph node sampling alone [Ref. 5].

Despite the recent advances in staging, post operative support and adjuvant chemotherapy, 40% of patients with stage I, 66% of stage II, and 75% of stage IIIA will still develop recurrence and die as a result of their disease within 5 years of resection [Ref. 14].

Residual micrometastases are believed to be the cause of disease recurrence. In an effort to eradicate micrometastases and improve overall survival (OS), numerous clinical trials have evaluated adjuvant and neoadjuvant chemotherapy.

1.2 Adjuvant chemotherapy for early stage NSCLC

Adjuvant chemotherapy is the standard treatment for patients with completely resected stage II or III NSCLC [Ref. 7].

A total of 23 randomized trials between 1992 and 2005 and five further meta-analyses have shown that adjuvant chemotherapy improves survival in patients with completely resected stage II and stage III disease. The Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group published a meta-analysis of five cisplatin-based trials in 2008. It included a total of 4,584 patients and demonstrated a 5.3% improvement in survival at 5 years with adjuvant chemotherapy (Hazard Ratio (HR)=0.89, 95% CI=0.82-0.96, P=0.0043). There was also an improvement in disease-free survival of 5.2% at 5 years (P<0.0001). The LACE meta-analysis also demonstrated that there was no association between chemotherapy effect and sex, age, histology, type of surgery, planned radiotherapy or planned total dose of cisplatin [Ref. 15]. Such results were also confirmed by a further meta-analysis with individual patient data from the same trials [Ref. 16].

The improvement in survival in patients with stage IB disease did not reach statistical significance and patients with stage IA disease appeared to do worse with adjuvant chemotherapy.

In the CALGB 9633 a total of 340 patients were randomly assigned to adjuvant chemotherapy or observation: no significant difference in survival (HR 0.83, 95% CI: 064-1.08, P=0.12) between the two groups was shown but the exploratory analysis demonstrated a survival advantage in the adjuvant chemotherapy group among those patients whose tumors were greater than or equal to 4 cm in diameter (HR 0.69, 95% CI: 0.48-0.99, P=0.043). Thus, the analysis of the CALGB group suggested that patients with stage IB disease with T ≥ 4cm may also benefit from adjuvant chemotherapy [Ref. 16]. A separate study, the JBR10 trial, showed similar results for stage IB disease: patients with tumors measuring >5 cm in diameter had a survival advantage when treated with adjuvant chemotherapy [Ref. 18].

NSCLC, all stage IA and those tumors in stage IB which are less than 4 cm remain an area where there is no standard therapy. Vinorelbine/cisplatin is the most commonly used doublet chemotherapy on the basis of the phase III adjuvant studies in NSCLC; other combinations commonly used are cisplatin/gemcitabine and carboplatin/paclitaxel. However, poor compliance due to toxicity has been a major issue in clinical trials of adjuvant therapy, with approximately only 45-50% of patients completing all 4 planned cycles at full planned dose.

Table 1. Randomized trials of adjuvant platinum-based chemotherapy

Trial	Patients N	Stage	Regimen	5y Survival Benefit (%)	p
ECOG 3590 [Ref. 19]	488	II-IIIA	Cisplatin Etoposide	0	0.56
ALPI [Ref. 20]	1209	I-IIIA	Cisplatin Mitomycin Vindesine	3	0.589
ANITA [Ref. 21]	840	IB-IIIA	Cisplatin Vinorelbine	9	0.017
JBR.10 [Ref. 18]	482	IB-II	Cisplatin Vinorelbine	15	0.04
IALT [Ref. 22]	1867	I-IIIA	Cisplatin Vindesine OR Vinblastine OR Vinorelbine OR Etoposide	4	0.1
BLT [Ref. 23]	381	I-IIIA	Cisplatin Vindesine OR Vinorelbine Cisplatin Mitomycin OR Ifosfamide OR Vinblastine	2	0.9
CALGB 9633 [Ref. 17]	344	IB	Carboplatin Paclitaxel	4	0.125

Recently, the RADIANT trial was presented at the ASCO meeting 2014. This was a trial with a 2:1 randomization of erlotinib versus placebo after radical surgery followed by adjuvant chemotherapy for stage IB, II, IIIA NSCLC patients: erlotinib did not significantly improve the median disease free survival (DFS) compared to placebo in the overall population (50.5 versus 48.2 months; HR=0.90, 95%CI=0.74-1.1) and did not show any OS benefit, even for the censored analysis (HR=1.09, 95%CI=0.54-2.16). However, an early improvement in DFS of the order of 18 months was seen in the Epidermal Growth Factor Receptor (EGFR) mutated subpopulation (HR=0.61, 95%CI=0.38-0.98).

As this was not the primary endpoint and in the context of the hierarchical statistical testing, this was not statistically significant [Ref. 24].

The MAGRIT study was a double-blind, placebo-controlled trial in patients with completely resected MAGE-A3-positive NSCLC Stages IB, II, and IIIA. Patients were randomized (2:1) to intramuscular injections of MAGE-A3 vaccine versus placebo. This study was presented at the 2014 ESMO Conference and was negative for its primary and secondary endpoints [Ref. 25].

Therefore, for stage II - IIIA operable patients with resectable disease at diagnosis, the standard treatment is still radical surgery (lobectomy/pneumonectomy) followed by up to 4 cycles of adjuvant chemotherapy with a platinum-based doublet, most commonly cisplatin plus vinorelbine.

For stage IB, the treatment is decided on the basis of the tumor size, greater than or equal to 4 cm tumors are treated as stage II and IIIA above and T less than 4 cm are offered no adjuvant chemotherapy after surgery.

The role of postoperative radiotherapy (PORT) is so far limited to patients with pathologic N2 disease or to those that have residual disease at the surgical resection [Ref. 26]. There is no added benefit of radiotherapy in the neoadjuvant setting [Ref. 27] and there seems to be a detrimental role for radiotherapy in stages I and II in the adjuvant setting [Ref. 28].

In the SEER database (population-based cohort) PORT use was associated with an increase in survival in patients with N2 nodal disease but not in patients with N1 and N0 nodal disease [Ref. 29].

Prospective data are awaited from the ongoing EORTC LUNGART study [Ref. 30].

1.3 Background data for Anti- PD1 and PDL1

The programmed death receptor 1 (PD-1) is a key immune checkpoint receptor expressed by activated T cells that modulates a late stage of the immune response by negatively regulating the activation of T cells in peripheral tissues. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. 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. 31, Ref. 32].

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. 32, Ref. 33, Ref. 34, Ref. 35].

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. 36]. 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. 37, Ref. 38]. 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. 39].

The ligands for PD-1 (PD-L1 (B7-H1) and PD-L2 (B7-DC)) are constitutively expressed or can be induced in a variety of cell types including non-hematopoietic tissues and in various tumors [Ref. 36, Ref. 40, Ref. 41, Ref. 42]. 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 PDL1 serves to dampen unwarranted T cell function in peripheral tissues [Ref. 36]. 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. 43], pancreatic carcinoma [Ref. 44], hepatocellular carcinoma [Ref. 45], and ovarian carcinoma [Ref. 46].

PD-L1 status was described in many cancer types and in particular in lung cancer where up to 50% of NSCLCs are reported to express PD-L1 [Ref. 47, Ref. 48]. High expressers of PD-L1 on immunohistochemistry of tumor samples appear to get the best benefit from PD-1 or PD-L1 inhibitors although the benefit is not exclusive to this group [Ref. 49].

Recent data presented at ESMO Conference [Ref. 49] in the advanced setting showed 37% strong positivity (defined as ≥50% membranous staining), 17% weak positivity (defined as 1-49% membranous staining) and 10% negativity. Median PFS and OS were longer for the strong positive cases versus the weak/negatives (HR=0.52 and 0.59, respectively). This is a dynamic field and the next few years will see development of the role of PD-L1 and other biomarkers.

1.4 Checkpoint inhibitors

Among the checkpoint inhibitors anti PD-1 and anti-PD-L1 mAbs have shown promising results in advanced NSCLC where they are currently being developed in phase I, II and phase III trials in first and subsequent lines of therapy [Ref. 50].

Two anti-PD-1 (nivolumab and pembrolizumab) and four anti-PD-L1 (BMS-936559, Medi-4736, MPDL3280A, MSB0010718C) antibodies have been investigated in phase I studies and are under further development in NSCLC [Ref. 50]. In all phase I trials, the maximum-tolerated dose was not reached, and all doses were found to be safe.

The frequency of immune-related toxicities from anti–PD-1/anti–PD-L1 treatments appears less than that from anti-CTLA4 treatment. The common drug-related AEs were decreased appetite, anemia, diarrhea, nausea, pruritus, fatigue, pneumonitis, and elevated transaminase [Ref. 51, Ref. 52, Ref. 53, Ref. 54, Ref. 55, Ref. 56].

Table 2. Clinical development of Immune Checkpoint Inhibitors - Efficacy Data on NSCLC

Target	Antibody	Molecule	Development stage	ORR All comers	Ref
PD-1	Nivolumab	Fully human IgG4	Phase III	24%	[Ref. 57]
	Pembrolizumab	Humanized IgG4	Phase III	21%	[Ref. 49]
PD-L1	BMS-936559	Fully human IgG4	Phase I - halted	-	[Ref. 58]
	MEDI-4736	Engineered human IgG1	Phase III	16%	[Ref. 59]
	Mpdl-3280A	Engineered human IgG1	Phase III	23%	[Ref. 60]
	MSB0010718C	Human IgG1	Phase I	NA	[Ref. 61]

1.5 Pembrolizumab characteristics and clinical data overview

Pembrolizumab is a highly selective humanized monoclonal antibody (mAb) that binds to the PD-1 receptor and directly blocks the interaction between PD-1 and its ligands, thereby enhancing tumor regression and ultimately immune rejection (see the IB). Pembrolizumab is being investigated in various oncology indications including melanoma, NSCLC, renal cell carcinoma (RCC), breast cancer, multiple myeloma (MM), microsatellite unstable tumors, and head and neck cancer. Pembrolizumab [Keytruda (US)], is approved for treatment of advanced (unresectable or metastatic) melanoma for adults in the US, EU and several countries. Pembrolizumab has also been granted approval in the US, EU and several countries for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

1.5.1 Preclinical studies

In cultured blood cells from healthy human donors, cancer subjects, and nonhuman primates pembrolizumab strongly enhanced T-lymphocyte immune responses. It potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells.

In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ) and levels of other cytokines were found to be modulated by pembrolizumab.

Using an anti-murine PD-1 surrogate antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these

experiments in mice, anti-PD-1 therapy was synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU), and combination therapy resulted in increased complete tumor regression rates in vivo.

In animal studies (cynomolgus monkeys), it was demonstrated that the systemic exposure to pembrolizumab, independently of sex, increased with increasing dose. Systemic exposure for the 7-day dosing interval increased after repeated dosing from 40 to 200 mg/kg. Area under the concentration-time curve (AUC) for the 7-day dosing interval after one dose appeared to be dose-proportional from 0.3 to 200 mg/kg, suggesting dose-independent pharmacokinetics (PK). Terminal half-life (t½) values from individual animals after repeated IV dosing ranged from 11.8 to 23.7 days (mean values ranged from 15.7 to 22.3 days) across the doses tested.

In cynomolgus monkeys pembrolizumab was well tolerated with systemic exposure over the course of the study and no significant in vivo toxicity was observed. In a 1-month and 6-month toxicology study, with IV pembrolizumab (up to 200 mg/kg) administered once a week and once every other week respectively, up to 200 mg/kg resulted in no adverse treatment related effects.

Additionally, in the tissue cross-reactivity study of pembrolizumab with human and monkey tissues the expected on-target staining of the membranes of mononuclear leukocytes in both species was demonstrated. Off-target cross-reactivity staining was also noted in both species but was limited to be considered related to the experimental method artifacts, i.e. tissue processing for IHC has 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).

1.5.2 Clinical studies

1.5.2.1 Phase I studies

An open-label Phase I trial (KEYNOTE-001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W), in participants with advanced solid tumors. All 3 dose levels were well tolerated and no dose-limiting toxicities were observed. Based on pharmacokinetic (PK) data showing a half-life of 21 days, the protocol was amended to change the dosing frequency in the expansion cohort to every 3 weeks (Q3W). All cohorts have completed enrollment.

In KEYNOTE-001, a total of 550 NSCLC participants were treated in several dose expansion cohorts with at least 1 dose of pembrolizumab. The initial data from 495 NSCLC participants have been published and reported. The ORR was 19.4% (18.0% in the 394 previously treated participants and 24.8% in the 101 previously untreated participants). The response rate (RR) was similar regardless of dose, schedule, and histologic analysis. Current or former smokers had a RR of 22.5%, as compared with 10.3% among participants who had never smoked cigarettes.

Participants were required to submit a newly obtained tumor biopsy prior to initiating therapy with pembrolizumab to evaluate the tumors for expression of PD-L1. After evaluation of several methods for pathological assessment, in a training set, membranous PD-L1 expression in at least 50% of tumor cells (TPS ≥ 50%) was selected as the cut-off point for defining PD-L1 as high. In a validation set of 313 participants, the RR was 45.2% in the 73 participants with a TPS ≥ 50%, including 43.9% in previously treated participants and 50% in previously untreated participants, values that numerically exceeded the RR in the training group.[Ref. 62].

Pembrolizumab has been generally well tolerated. The most common treatment-related AEs were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). Adverse events of Grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related AEs of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy [Ref. 62].

KEYNOTE-011 is a study currently ongoing in Japan, with a two stage design: in the first stage pembrolizumab as single agent will be tested for dose finding; in the second stage pembrolizumab in combination with either cisplatin/pemetrexed or carboplatin/paclitaxel in advanced NSCLC to assess safety and tolerability of the combination therapy [Ref. 63].

KEYNOTE-021 Pembrolizumab has been studied in combination with other agents in NSCLC patients in KEYNOTE-021. This Phase I/II trial assessed the safety and efficacy of pembrolizumab in combination with multiple therapeutic agents including chemotherapy (carboplatin and pemetrexed; and carboplatin, paclitaxel, and bevacizumab); EGFR inhibitors including erlotinib and gefitinib; and the CTLA-4 inhibitor, ipilimumab. Cohort G of the study evaluated the efficacy and safety of pembrolizumab plus carboplatin and pemetrexed (CP) vs. CP alone as first-line therapy for advanced non-squamous NSCLC.

KEYNOTE-021 Cohort G contained 123 participants of whom 60 were accrued to the pembrolizumab plus CP arm and 63 to the CP arm. Demographics were generally balanced between treatment arms. As of Aug 8, 2016, median follow-up was 10.6 months (range, 0.8-19.3); median exposure was 8.0 months for pembrolizumab plus CP and 4.9 months for CP. In the CP arm, 43 participants discontinued therapy; 32 received subsequent anti-PD-1 therapy as part of crossover (n = 20) or off study (n = 12). Pembrolizumab plus CP significantly improved ORR (55% vs. 29%; P = 0.0016) and PFS (HR 0.53, 95% CI 0.31-0.91, P = 0.0102; median 13.0 vs. 8.9 months). Overall survival was similar; 6-month survival rates were 92% in each arm. Without adjusting for exposure, for pembrolizumab plus CP vs. CP, treatment-related AEs led to discontinuation in 10% vs. 13%, were of grade ≥ 3 severity in 39% vs. 26%, and led to death in 2% (sepsis, n = 1) vs. 3% (sepsis and pancytopenia, n = 1 each). The most common any-grade treatment-related AEs were fatigue (64% vs. 40%), nausea (58% vs. 44%), and anemia (32% vs. 53%). [Ref. 64].

Finally **KEYNOTE-025** is an ongoing open-label, non-randomized, multi-center phase Ib study of pembrolizumab 10 mg/kg IV Q3 weeks in pretreated patients with PD-L1 positive advanced NSCLC in Japan [Ref. 65].

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.

Pembrolizumab has been generally well-tolerated. The most common treatment related adverse events were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). Adverse events of grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related adverse events of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy [Ref. 62].

1.5.2.2 Phase II and III studies

Pembrolizumab has been studied for various oncology indications, the most relevant in melanoma. In lung cancer specifically, several studies are ongoing, among them:

KEYNOTE-010 was a randomized, adaptively designed Phase II/III trial of pembrolizumab at 2 dose levels versus docetaxel in participants with NSCLC with PD-L1 positive tumors who had experienced disease progression after platinum containing systemic therapy. Participants were randomized according to their TPS (extent of PD-L1 expression) defined as follows: a TPS ≥ 50% was considered strongly positive and a TPS = 1% to 49% was considered weakly positive. Approximately 920 participants were planned to be enrolled in this trial to examine the efficacy of pembrolizumab compared to docetaxel in an enriched population.

Overall, the results from KEYNOTE-001 and KEYNOTE-010 demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. The PD-L1 selection employed in KEYNOTE-010 identified patients more likely to benefit from pembrolizumab and resulted in favorable hazard ratios (HR) in OS compared to docetaxel.

In previously treated participants with NSCLC with PD-L1, TPS ≥1%, and disease progression following platinum-containing chemotherapy, pembrolizumab provides a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy.

In KEYNOTE-010, pembrolizumab was superior to docetaxel in the strongly positive TPS ≥ 50% stratum with regard to OS, with an HR of 0.54 (p = 0.00024) and 0.50 (p = 0.00002) for pembrolizumab 2 mg/kg Q3W versus docetaxel and 10 mg/kg Q3W versus docetaxel, respectively. Pembrolizumab was superior to docetaxel in the overall positive TPS ≥ 1% population with regard to OS, with an HR of 0.71 (p = 0.00076) and 0.61 (p<0.00001) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively. Pembrolizumab was superior to docetaxel in the strongly positive TPS ≥ 50% stratum with regard to PFS by independent review committee based on RECIST 1.1, with an HR of 0.58 (p = 0.00009) and 0.59 (p = 0.00007) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively, compared to docetaxel. Pembrolizumab provided numerically superior benefit in PFS by

independent review committee based on RECIST 1.1 compared to docetaxel in the overall positive TPS ≥ 1% population, with an HR of 0.88 and 0.79 for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively; however, the differences were not statistically significant at the 0.001 level required per protocol. [Ref. 84].

Adverse events were as expected for pembrolizumab and docetaxel. Adverse events of special interest based on their likely immune aetiology, irrespective of attribution to study treatment, occurred in 69 (20%) of 339 patients in the pembrolizumab 2 mg/kg group and 64 (19%) of 343 patients in the pembrolizumab10 mg/kg group. The most common of these events were hypothyroidism, hyperthyroidism, and pneumonitis . The only adverse events of special interest of grade 3–5 severity that occurred in 1% or more of patients were pneumonitis and severe skin reactions [Ref. 84].

Overall, pembrolizumab prolongs overall survival and has a favorable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. KEYNOTE-010 has been submitted as the confirmatory study for the accelerated approval in NSCLC granted based upon results observed in KEYNOTE-001. [Ref. 66].

KEYNOTE-024 was a multicenter, international, randomized, open-label, controlled trial of intravenous (IV) pembrolizumab monotherapy versus the choice of multiple standard of care (SOC) platinum based chemotherapies in participants previously untreated for their Stage IV NSCLC and whose tumors expressed PD-L1 at ≥ 50%.

First-line treatment with pembrolizumab significantly prolonged PFS (HR 0.50; 95% CI: 0.37, 0.68; p<0.001) and OS (HR 0.60; 95% CI: 0.41, 0.89; p = 0.005) compared with SOC chemotherapy, inclusive of pemetrexed maintenance for participants with non-squamous tumors.

In addition, pembrolizumab was associated with a higher ORR, including a higher CR rate, as well as a longer DOR as compared to SOC.

Pembrolizumab was better tolerated than chemotherapy and AEs were easily managed. The observed safety profile of the pembrolizumab arm was consistent with the safety profile for pembrolizumab established to date. Based on the mechanism of action of pembrolizumab, immune-mediated AEs including pneumonitis occurred at a greater frequency with pembrolizumab compared to chemotherapy. Most immune-mediated events were of Grade 1 or 2 severity, and none led to death.

These data underscore the substantial benefit of pembrolizumab as initial therapy for participants with previously untreated, advanced NSCLC whose tumors express high levels of PD-L1 (TPS ≥ 50%) [Ref. 67].

KEYNOTE-042 is a multicenter, international, randomized, open-label, controlled trial of IV pembrolizumab versus SOC platinum-based chemotherapy in participants previously untreated for their advanced or metastatic NSCLC and whose tumors express PD-L1 ≥ 1%.Approximately 1240 participants will be enrolled [Ref. 68].

1.6 Rationale

Survival of completely resected NSCLC remains poor [Ref. 69].

The benefit of adjuvant chemotherapy in NSCLC is 5.4% in OS at 5 years with the regimens most commonly used, which also induce toxicities that have a major impact on the treatment tolerability.

Recent clinical trials assessing the use of the MAGE A3 vaccines have failed to demonstrate any improvement in efficacy. The RADIANT trial of erlotinib in the EGFR mutated subgroup, suggests that this treatment may improve DFS in EGFR mutated tumors, but not affect OS. Therefore there is a need to identify new treatment strategies that can increase the efficacy of adjuvant treatment.

Although first-generation immunotherapies in advanced disease were of limited efficacy, they provided proof-of-concept that, in some patients, the immune balance could be shifted in favor of tumor elimination. Expanding knowledge and understanding of the immune system's role in cancer have revealed multiple mechanisms by which tumors evade immune destruction. In particular, negative regulatory pathways involved in the T-cell-mediated response, including interaction of PD-1 and PD-L1, appear to have a role in tumor progression.

Checkpoint inhibitors have demonstrated benefits with a reasonable safety profile/tolerability in lung cancer in the advanced setting.

Theoretically, immunotherapy should work best in the situation of minimal residual disease. The adjuvant setting is therefore the ideal clinical scenario to test the true place of immunotherapy with these new agents and potentially improve the cure rate after surgery.

This study will be a randomized trial in NSCLC patients after surgery and completed adjuvant treatment comparing adjuvant pembrolizumab versus placebo.

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). The initial dose approved by the Food and Drug Administration (FDA) for treatment of melanoma subjects was 2 mg/kg Q3W. Currently, clinical trials evaluating pembrolizumab are using a fixed dose of 200 mg Q3W. The use of a fixed dose is based on PK findings summarized below.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other subject covariates on exposure using available data from 1139 subjects (from Keynote-001 and Keynote-002) has been performed. The majority of these subjects (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose, and importantly, maintained individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the

antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types.

2 Objectives of the trial

2.1 Primary/dual-primary objectives

To prospectively investigate whether adjuvant treatment with pembrolizumab after completion of radical surgery (lobectomy/pneumonectomy) with or without standard adjuvant chemotherapy for stage IB (T ≥ 4 cm) -II-IIIA NSCLC patients improves Disease Free Survival (DFS), as assessed locally by the investigator, compared to placebo in the PD-L1 strong positive subgroup or overall population.

Note: TNM stage (according to the 7th edition of the TNM classification for lung cancer)

2.2 Secondary objectives

- To prospectively compare DFS as assessed by the investigator in the PD-L1 positive population (TPS≥1%);
- To prospectively determine and compare OS in the PD-L1 strong positive and overall population;
- To prospectively determine and compare OS in the PD-L1 positive population;
- To prospectively determine and evaluate the Lung Cancer Specific Survival (LCSS) in the whole population irrespective of PD-L1 status;
- To prospectively assess the safety of pembrolizumab after radical surgery followed by standard adjuvant chemotherapy.

2.3 Exploratory Objectives

CCI

2.4 End-points

2.4.1 Primary/dual-primary endpoints

- DFS in the PD-L1 strong positive subgroup;
- DFS in the overall population.

With the use of primary and dual-primary endpoints, if either of the tests in the primary or dual-primary endpoint is significant, then the study can be declared successful in their respective population or sub-population.

2.4.2 Secondary endpoints

- DFS in the PD-L1 positive population;
- OS in the overall population;
- OS in the PD-L1 strong positive subgroup;
- OS in the PD-L1 positive population;
- LCSS in the overall population;
- Toxicity according to CTCAE version 4.03.

2.4.3 Exploratory endpoints

- Health-Related Quality of Life (HRQOL);
- Pharmacokinetics (PK) of pembrolizumab in this patient population;
- Anti-drug antibiodies (ADA) against pembrolizumab (immunogenicity evaluation);
- Quality assurance for surgery;
- Exploratory assessment of predictive biomarkers and immune dynamics (Translational research).

3 Patient selection criteria

Patient enrollment will follow a three-step procedure as illustrated in Chapter 4 (step 1 registration, step 2 central confirmation of PD-L1 status, step 3 randomization). Patients must meet all of the criteria described in Sections 3.1, 3.2 and 3.3 to be eligible for randomization in step 3.

3.1 Registration - step 1 (ORTA step 1)

Before patients registration, written informed consent for tumor testing must be given according to ICH/GCP and national/local regulations. For patients that accept to participate in the translational research, we recommend the informed consent for translational research to be signed before registration step 1.

3.1.1 Disease status

- Pathological diagnosis of NSCLC confirmed at surgery, any histology is eligible;
- Confirmed UICC v7 stage IB with T ≥ 4 cm, II-IIIA NSCLC after complete surgical resection (lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy) as documented in the pathology report;

Note: TNM stage according to the 7th edition of the TNM classification for lung cancer

- Resection margins proved microscopically free (R0); Resection margins are evaluated at the bronchial, venous and arterial stumps, peribronchial soft tissue, any peripheral margin near the tumor or of additionally resected tissue;
- A systematic complete mediastinal lymph node dissection or a lobe-specific mediastinal lymph node dissection (Appendix K) is recommended. At a minimum, the pathology and/or operative report must include the examination of at least two different mediastinal lymph node (N2) levels, one of which is the subcarinal (level 7) and the second of which is lobe-specific.
- In the uncommon clinical situation where the surgeon thoroughly examines a particular mediastinal lymph node level and does not find any lymph nodes, that mediasintal lymph node level may be counted among the minimum two required levels. However, the surgeon **must** clearly document in the operative report or in a separate written statement that the lymph node level was explored and **no** lymph nodes were present. Normal appearing lymph nodes, if present, must be biopsied or/removed.
- No extracapsular extension of tumor in resected mediastinal (N2) lymph nodes. Extracapsular tumor extension is permitted in resected N1 lymph nodes;
- The highest mediastinal node removed can be positive for malignancy;
- Carcinoma in situ can be present at bronchial margin.
- Patients with two synchronous primary non-small cell lung cancers are excluded from the study.

- Availability of tumor sample obtained at surgical resection for PD-L1 Immunohistochemistry (IHC) expression assessment. The tumor sample must be shipped for PD-L1 IHC expression testing at a central pathology laboratory. Please refer to the laboratory manual for further details. Patients will be eligible to participate regardless of the level of PD-L1 status, however tissue must be considered satisfactory for characterization of PD-L1 status.

- Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides must be freshly cut and submitted to the central testing laboratory;
- Patients whose samples are inadequate for PD-L1 determination will not be enrolled.

3.1.2 Patient status

- At least 18 years;

3.2 Central confirmation of PD-L1 status - step 2

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

3.3 Randomization - step 3 (ORTA step 2)

Before patient randomization, written informed consent ('Main Study') for participation in the study must be given according to ICH/GCP, and national/local regulations.

3.3.1 Disease status

- No evidence of disease (NED) at clinical examination and baseline radiological assessment as documented by contrast enhanced chest/upper abdomen CT scan, brain CT/MRI and clinical examination within 12 weeks prior to the randomization date.

3.3.2 Patient status

- ECOG Performance status 0-1;
- Adequate organ function performed within 10 days of treatment initiation and defined as follows:

Table 3. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,5 x 10^9/L
Platelets	≥100 x 10^9/L
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)	≤ 1.5xULN OR ≥ 30 mL/min for subject with creatinine levels >1.5x institutional ULN

System	Laboratory Value
Hepatic	
Total bilirubin	≤ 1.5xULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤ 2.5xULN
a Creatinine clearance should be calculated per institutional standard. b. For patients with Gilbert's disease total bilirubin may be > 1.5 x ULN, however direct bilirubin must be normal	

- Adjuvant chemotherapy is not mandatory but considered for patients with stage IB (T ≥ 4 cm) and strongly recommended for stage II and IIIA, and will be administered according to national and local guidelines. Patients who received more than 4 cycles of adjuvant therapy are not eligible;
  - Patients not receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date.
  - Participants who receive adjuvant chemotherapy must begin adjuvant chemotherapy within 12 weeks of their surgery date. Patients receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo at least 3 weeks but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle).
- No prior or planned neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy is allowed;No prior treatment with anti-PD-1, anti-PD-L1/2, anti-CD137, CTLA-4 modulators or any other immune-modulating agents; patients receiving live vaccine within 30 days prior to the first infusion of study treatment are not eligible;
- No current participation in an interventional clinical trial or treatment with an investigational agent or use of an investigational device within 4 weeks of the first infusion of study treatment;
- No known history of Human Immunodeficiency Virus (HIV) (known HIV 1/2 antibodies positive). No known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA result greater than the lower limits of detection of the assay;
- No chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 3 days prior to the first infusion of study treatment:
  - Corticosteroid use on study for management of ECIs (Pembrolizumab Event of Clinical Interest), as pre-medication for the administration of chemotherapies, and/or a premedication for IV contrast allergies/reactions is allowed;
  - Daily prednisone at doses of 5-7.5 mg is allowed as an example of replacement therapy. Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy;

- No history of interstitial lung disease (ILD) OR a history of (non-infectious) pneumonitis that required oral or IV steroids (other than COPD exacerbation) or current pneumonitis.
- 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). Any replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. Patients with hyperthyroidism or hypothyroidism but that are stable on hormone replacement are also allowed.
- No history of a hematologic or primary solid tumor malignancy, unless in remission for at least 5 years. A pT1-2 prostatic cancer Gleason score < 6, superficial bladder cancer, non melanomatous skin cancer or carcinoma in situ of the cervix is eligible;

Note: prior radiotherapy for another malignancy (breast cancer, lymphoma, germ cell tumor, etc.) is not an exclusion criterion, the same applies for prior anti-cancer systemic chemotherapy

- No previous allogeneic tissue/solid organ transplant;
- No active infection requiring therapy;
- No surgery or chemotherapy related toxicity (non-hematological toxicity resolved to grade 1 (see Appendix D), with the exception of alopecia, fatigue, neuropathy and lack of appetite /nausea);
- Female patients with childbearing potential must have a negative urine or serum pregnancy test at screening (within 72 hours of first infusion of study medication). If the urine test cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as (by other than medical reasons):
  - ≥45 years of age and has not had menses for greater than 1 year,
  - Amenorrheic for > 2 years without a hysterectomy and oophorectomy and an FSH value in the postmenopausal range upon pretrial (screening) evaluation,
  - Whose status is post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last infusion of study treatment. Information must be captured appropriately within the site's source documents.
- If of childbearing potential, female patients must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last infusion of study treatment (see Appendix L).

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Please refer to Appendix M for recommendation based on Clinical Trial

Facilitation Group guidelines for sites and countries where applicable (e.g. United Kingdom, Norway, Sweden, Portugal, etc.).

- Male patients with a female partner(s) of child-bearing potential must agree to use two adequate barrier methods throughout the trial starting with the screening visit through 120 days after the last infusion of study treatment is received (see Appendix L). Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Please refer to Appendix M for recommendation 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 must discontinue nursing prior to the first infusion of study medication and until 120 days after the last study treatment;
- Absence of severe comorbidities that in the opinion of the Investigator might hamper the participation to the study and/or the treatment administration;
- Patients not receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date. Participants who receive adjuvant chemotherapy must begin adjuvant chemotherapy within 12 weeks of the surgery date. Patients receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo at least 3 weeks but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle).

After the enrollment step in ORTA, patients will be automatically randomized in the Interactive Voice Response System (IVRS).

Important note: An additional +2 day window is allowed for randomization. All eligibility criteria must be adhered to.

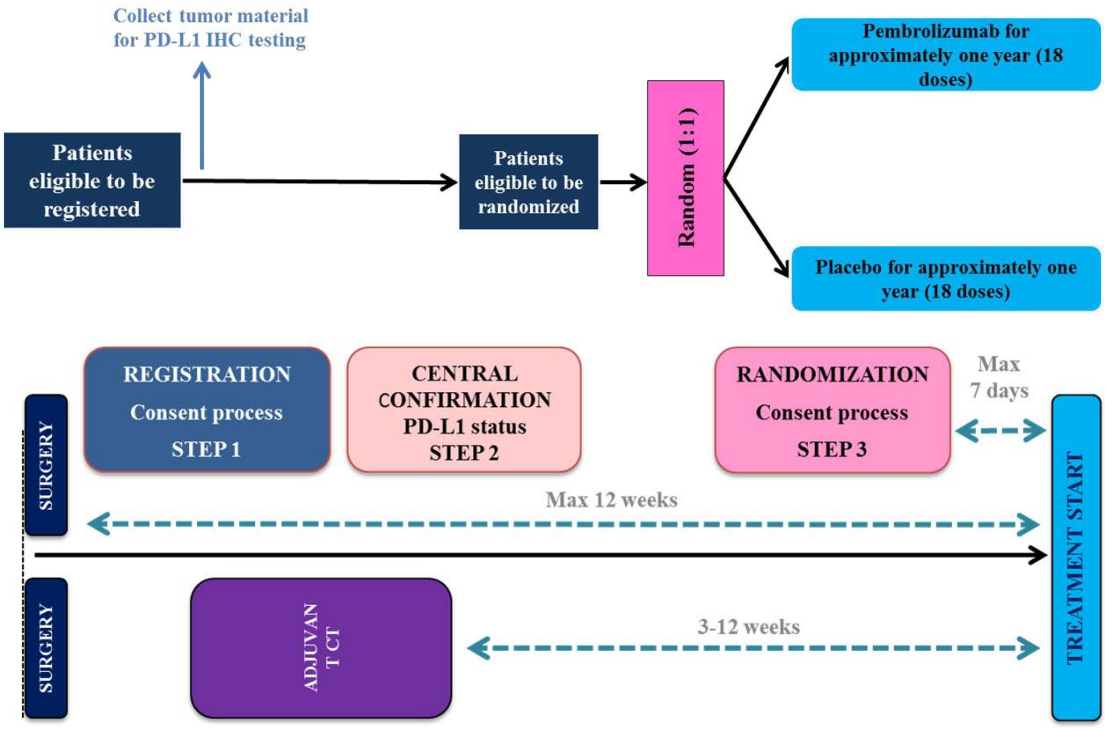
4 Trial Design

This is an international, triple-blinded, placebo-controlled randomized phase III trial.

4.1 Multi step process for enrollment

Enrollment of patients will follow a three-step informed consent process.

Figure 1: Trial design



4.1.1 Registration - step 1 (ORTA step 1)

Upon signing the informed consent, patients will be registered and a sample of the resected tumor will be shipped and evaluated for PD-L1 status at a central pathology laboratory.

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. If the sample is inadequate for analysis, another sample could be provided or the patient will be considered ineligible for further randomization in the trial.

4.1.2 Central confirmation of PD-L1 status - step 2

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

4.1.3 Randomization - step 3 (ORTA step 2)

The confirmation of PD-L1 status 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. Patients who are not receiving adjuvant chemotherapy can sign the main consent concurrently with the PD-L1 informed consent or after the results of the PD-L1 status are known. Patients receiving adjuvant chemotherapy may sign the main informed consent after completing chemotherapy.

Once patients are confirmed to be eligible through ORTA they will be automatically randomized in the Interactive Voice Response System (IVRS). For all patients, dosing must occur within 7 days of randomization.

A total of 1180 eligible patients will be randomized at 1:1 ratio into two triple blinded,treatment arms (approximately 590 patients each):

- Patients in one arm will receive pembrolizumab (see Sections 5.2 and 5.4);
- Patients in the other arm will receive placebo (see Sections 5.1 and 5.4).

Patients not receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date. Participants who receive adjuvant chemotherapy must begin adjuvant chemotherapy within 12 weeks of their surgery date. Patients receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo at least 3 but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle). Randomization will be performed centrally (see Chapter 14) and will be stratified for the following factors:

- Stage (IB vs II vs IIIA);
- Adjuvant chemotherapy (no adjuvant chemotherapy versus adjuvant chemotherapy);
- PD-L1 status: negative (TPS=0%) versus weak positive (TPS=1-49%) versus strong positive (TPS≥50%);
- Region (Western Europe versus Eastern Europe versus the Rest of the world versus Asia)

The proportion of patients with stage IB will be closely monitored by the study steering committee to ensure that this proportion does not exceed 35% of the study population.

This is a triple blind study according to the CDISC Clinical Research Glossary Version 8.0. The patient, the investigator and study team at site (an on-site pharmacist will remain unblinded to treatment assignment), and the EORTC Headquarters study team will remain blinded to treatment allocation up to the database lock for the final analysis of the primary/dual-primary endpoints.

However, 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.

Please see Section 14.6 for Unblinding Procedures

The exploratory parameters in this study will be refined according to the current knowledge in the field during trial advancement and at the time of trial completion.

4.2 Unblinding data

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

- Emergency Unblinding
- Unblinding by Investigator Request After Disease Recurrence
- Unblinding at Final Analysis
- Other Unblinding During the Course of the Study

Please see Section 14.6 for Unblinding Procedures

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.

(Note specific to Japan): normal saline solution used as a placebo is not considered an investigational product defined by the Japan's Pharmaceutical and Medical Devices Act.

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

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

Clinical data from eight randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W);

Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications; and

Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W.Among the eight randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs 10 mg/kg Q3W (KN001 B2,

KN001 D, KN002, KN010 and KN021), and three studies compared 10 mg/kg Q3W vs 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

5.3 Drug supply

The pharmacist 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 not be provided by MSD but will be provided by the Investigational sites and prepared by the local unblinded pharmacist.

5.3.2 Pembrolizumab

Pembrolizumab will be provided by MSD.

5.3.2.1 Initial drug supply

Refer to Pharmacy Manual.

5.3.2.2 Drug resupply by IVRS

Refer to the IVRS Manual.

5.3.3 Packaging, labeling, handling and storage

5.3.3.1 Packaging

Packaging and labeling of Pembrolizumab and placebo 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 MSD in vials of 50 mg lyophilized powder or in 100 mg liquid vials.

Details on the infusion preparation and administration are provided in the Pharmacy Manual.

5.3.3.4 Storage

Investigational product must 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 subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

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

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

5.3.4 Drug accountability

The pharmacist is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator 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, the amount returned, and the amount received from and returned to MSD, when applicable.

5.3.5 Return of investigational product

The pharmacist is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed and returned 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 pharmacist is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by 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 pharmacist 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) to allocate patients, to assign treatment to patients and to manage the distribution of clinical supplies. Each person accessing the IVRS 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

Pembrolizumab/Placebo at a dose of 200 mg, administered intravenously (IV), every 3 weeks, for a total of 18 infusions, approximately one year.

Note: if visits are missed and/or delayed treatment will continue beyond 1 year in order to complete 18 infusions.

5.5 Treatment duration

In both arms, treatment will be administered for a maximum of 18 infusions for approximately one year, unless one of the withdrawal criteria applies (see Section 5.6). In case of delay in scheduled administration, the treatment can continue beyond 1 year in order to complete the 18 infusions.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or discontinue treatment.

In this trial, a subject may discontinue from study treatment for the reason outlined below but will remain in the trial for follow up as outlined in Section 6.7, as long as the subject does not withdraw consent. Discontinuation from study treatment is permanent. Once a subject has discontinued study treatment for the reason outlined below, he/she shall not be allowed to begin study treatment again (This is distinct and different from infusion / treatment delays required due to adverse events. For guidelines for management of toxicity and schedule modification and supportive care guidelines please refer to Appendix G and Appendix H). A subject should stop the study treatment (but should be encouraged to continue to be monitored/followed-up in the trial) for any of the following reasons:

- The subject or legal representative (such as legal guardian) withdraws consent;
- Disease recurrence by RECIST version 1.1;

- Unacceptable adverse events;
- The subject's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that require active treatment;
- Inter-current illness (including second malignancy) that, in the opinion of the investigator, warrants the patient's withdrawal from study treatment;
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AE in Appendix G and Appendix H.
- Investigator's decision to withdraw the subject;
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The subject has a positive pregnancy test or is pregnant;
- Noncompliance with trial study treatment or procedure requirements;
- Administrative reasons.

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events). Events of Clinical Interests (ECIs) will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy. Subjects will have post-treatment follow-up specified in Section 6.7.

5.7 Management of toxicity

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

5.8 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 case report form (CRF) including all prescription, over-the-counter (OTC), 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 CRF.

All concomitant medications received within 30 days before the first infusion of study treatment and 30 days after the last infusion of study treatment must be recorded.

5.8.1 Prohibited medications

- Any concurrent anti-cancer treatment (surgery, radiotherapy, systemic therapy);
- Any investigational agents;

- Immunosuppressive agents (except for patients treated for irAE);
- Immune-modulating agents
- Chronic systemic corticosteroids, with equivalents of more than 7.5mg of prednisone (except for patients which during the study developed endocrinopathies requiring stable doses of hormone replacement therapy such as hydrocortisone);
- Steroid premedications for contrast CTs are permissible;
- Live vaccines within 30 days prior to the first infusion of study therapy and while participating in study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine.

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 6.8 summarize the trial procedures to be performed at each visit. Chest and upper abdomen CT scan to assess disease status are mandatory. PET alone will not be used for the disease assessment.

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

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.

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 trial medication/vaccination in emergency situations where the investigator is not available.

6.2 Before treatment start

- Eligibility criteria (see Section 3.1);

A specific informed consent ('Registration') has been prepared to send the tumor sample for thePD-L1 status and must be signed by the patient before shipment of the tumor. This is mandatory. At the same time the consent for the optional Translational Research (TR) ('Biomedical Research') will be presented to the patient (see Section 6.5).This consent must be signed before any additional TR samples are collected. It is recommended patients sign the TR ICF along with Registration to collect Step 1 samples. However, the patient can reconsider taking part in the optional TR at a later stage during the trial. The Main informed consent will be signed during the referral period after the surgery if no adjuvant chemotherapy is foreseen or at the end of standard adjuvant chemotherapy. This consent must be signed before any additional TR samples are collected.

- Whole blood for germline (20 mL) and serum (20 mL) (during Step1)
- Whole blood for correlative DNA, whole blood for correlative RNA, PBMC (for selected sites in Spain, France and Switzerland only, during Step 3)

6.2.1 Within 12 weeks prior to randomization

The patient's written informed consent ('Main Study') 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) and collection of HQRoL,.

Upon confirmation of the PD-L1 status and (‘Main Study’) written informed consent, the following exams will be performed during the screening phase (maximum of 12 weeks from ICF signature until the randomization) and results must be known before randomization:

- Eligibility criteria (see Section 3.3);
- Demographics, medical history, height and smoking status;
- HIV, HBV, HCV serology (Active Hepatitis B is defined as a known positive HBsAg result. Active; active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay) if clinically indicated according to the local investigator;
- Physical examination (including heart rate, blood pressure, weight and temperature);
- 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 must be performed:

- Contrast-enhanced chest and upper abdomen CT scan;
- Contrast-enhanced brain CT scan or MRI;

- Concomitant medications assessment;
- Adverse event assessment;
- HRQoL evaluations : EORTC QLQ-C30 version 3, EORTC QLQ-LC13 and EQ-5D;

Please refer to Table 4 in Section 6.8.1.

6.2.2 Within 10 days prior to treatment initiation

- Hematology: white blood cell count (WBC), absolute neutrophils count (ANC), lymphocytes, eosinophils, basophils, monocytes, red blood cell count (RBC), hemoglobin (Hgb), haematocrit (Hct), platelets;
- Serum chemistry: creatinine, urea or blood urea nitrogen (BUN), total bilirubin*, AST, ALT, alkaline phosphatase, LDH, tot proteins, potassium (K), sodium (Na), calcium (Ca), bicarbonate (HCO_3) (HCO_3 testing could be optional in countries where testing is not standard of care), albumin and glucose.

* If total bilirubin levels >1.5xULN, direct bilirubin must be collected.

Please refer to Table 4 in Section 6.8.1.

Note: hematology and serum chemistry are to be repeated if performed more than 10 days prior to the first infusion of study treatment.

6.2.3 Within 72 hours prior to treatment initiation

- Pregnancy test: serum (or urine) beta HCG in fertile female study participants. This pregnancy test is to be renewed/repeated during protocol treatment at least monthly or more frequently if required by national regulations/institution guidelines

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

6.2.4 Within 24 hours prior to treatment initiation

- Pharmacokinetics: one blood sample of 3.5 mL;
- Anti-pembrolizumab antibody (ADA): one blood sample of 6 mL;
- Additional PK and ADA samples will be collected at subsequent infusions outlined in study;

Please refer to in Section 6.8.3.

6.3 During treatment

Pregnancy test: serum (or urine) beta HCG in fertile female study participants. This pregnancy test is to be renewed/repeated during protocol treatment at least monthly or more frequently if required by national regulations/institution guidelines.

Infusion schedule

1) Normal schedule

Window of administration is up to 3 days before or after the scheduled day of each infusion, due to administrative reasons, except for infusion 1 where the window is + 7 days from randomization.

2) Delayed infusions

Definition of **delayed** infusion: an infusion is considered as delayed if administration occurs at least 3 days after the theoretical date, but less than 10 days after the theoretical date. Future infusion dates should follow every 3 weeks, calculated from the actual date of administration of the delayed infusion. If **infusion is delayed** (e.g. patient on holiday, adverse events, hospitalized, etc) the site must:

- 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 date of infusion.
- Follow calendar days for imaging assessment and not adjust for delays. The reference date for imaging scans must be the date of the first infusion (infusion 1).

3) Missed infusions

Definition of **missed** infusions: an infusion is considered as missed if administration would occur more than 10 days after the theoretical date. In this case, no infusion is given. The next ainfusion should occur as soon as the cause of the missed infusion is resolved and not delayed until the next scheduled infusion. Future infusion dates should follow every 3 weeks, calculated from the actual date of administration of the delayed infusion.

If **infusion administration is missed** (e.g. toxicity, delay greater than 10 days, etc), the site must:

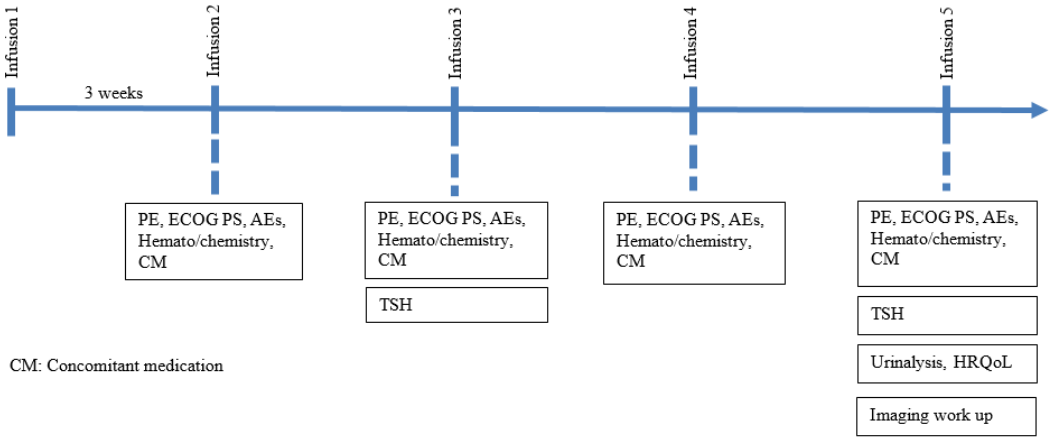
- Complete all protocol required laboratory tests, physical exam, adverse events assessments, concomitant medication assessments and HRQoL assessments within the required window prior to the **missed** date of infusion administration. If a visit did not occur, documentation is required (see CRF completion guidelines).
- Follow calendar days for imaging assessment and do not adjust for delays. The reference date for imaging scans must be the date of the first infusion (infusion 1).

Due to missed infusions, completion of 18 infusions will extend beyond 1 year and must be assessed as per protocol Section 6.3.

The visits for evaluations described below refer to study drug administrations.

It is therefore expected that results of laboratory (hematology, serum chemistry, thyroid, urinalysis) and imaging results are available prior to study drug administrations and within required timelines every 3 weeks (+/- 3 days), every 6 weeks (+/- 3 days) and every 12 weeks (+/- 3 days or +/- 2 weeks) depending on the type of evaluation.

Figure 2: Overview schedule of test/exams



6.3.1 Every 3 weeks (+/- 3 days)

Before each infusion, the following exams will be performed every 3 weeks and laboratory results must be available prior to study drug administration:

- Physical examination / ECOG performance status see Section 6.2.1;
- Assessments of adverse events;
- Hematology and serum chemistry see Section 6.2.2;
- Concomitant medication assessment

Please refer to Table 4 in Section 6.8.1.

6.3.2 Every 6 weeks (+/- 3 days)

The following test will be performed every 6 weeks and results must be available prior to study drug administration:

- Thyroid function: TSH; in case of elevated TSH to add free T3 (or total T3) and free T4;

Please refer to Table 4 in Section 6.8.1.

6.3.3 Every 12 weeks (+/- 3 days)

In addition to the above, an urinalysis will be performed as per Section 6.2.1 and results must be available prior to study drug administration.

HRQoL questionnaires will be collected: EORTC QLQ-C30 version 3, EORTC QLQ-LC13 and EQ-5D

- Questionnaires are filled in every 12 weeks (+/- 3 weeks) during the first year (starting on day 1 infusion 1). HRQoL data must be collected regardless of the patient's progression status.

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 Section 5.7.

Please refer to Table 4 in Section 6.8.1.

6.3.4 Every 12 weeks (+/- 2 weeks) starting from the day of first infusion (visit 1) and until disease recurrence

Imaging work up (to be based on calendar and not adjusted for delays or missed treatment):

- Contrast-enhanced chest and upper abdomen CT scan;
- Contrast-enhanced brain CT scan or MRI only if clinically indicated (new evidence of headache or neurologic symptoms);

Note: Patients who receive treatment beyond 1 year from randomization, (to compensate for missed or delayed doses), should have imaging performed every 12 weeks (+/- 2 weeks) until discontinuation of treatment and then will follow Section 6.7 (Follow-up).

Please refer to Table 4 in Section 6.8.1.

6.4 End of Treatment

At the time of early study withdrawal or withdrawal of consent, the reason for early withdrawal and any new or ongoing AEs must be documented in the applicable e-CRFs.

End of treatment visit will occur at the treatment discontinuation due to 1) completion of planned therapy in the protocol 2) disease recurrence or 3) treatment discontinuation due to reasons outlined in Section 5.6.

In case of discontinuation prior to the first treatment infusion, the baseline visit can take place as end of treatment visit. Therefore only an end of treatment form must be additionally completed to record reason for discontinuation.

The following exams will be performed at 4 weeks (± 2 weeks) after the last infusion administration:

- Physical examination/ECOG performance status;
- Assessment of AEs; if at the time of treatment discontinuation, the patient suffers from a severe Grade 3 or 4 AE, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible;
- Concomitant medication assessment;
- Hematology and serum chemistry see Section 6.2.2;
- Urinalysis see Section 6.2.1;
- Thyroid function: TSH; in case of elevated TSH to add free T3 (or total T3) and free T4;

- Disease evaluation (see imaging work-up Section 6.3.4): only in case of discontinuation in absence ofdisease recurrence;
- HRQoL evaluations : EORTC QLQ-C30 version 3, EORTC QLQ-LC13 and EQ-5D.

Please refer to Table 5 in Section 6.8.2. **Note**: Patients discontinuing treatment 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.

6.5 Translational research

In the frame of a proposal for Translational research the following samples will be collected for patient who consented. Please refer to Table 6, Chapter 11 and Laboratory manual for additional information on amount of material required, collection timepoints and potential research purposes.

6.6 Pharmacokinetic and anti-pembrolizumab antibody

Pre-infusion trough PK (3.5 mL each) and ADA (6 mL each) samples will be collected **before administration of pembrolizumab/placebo** at the following timepoints:

- Before infusion 1, infusion 2, infusion 4, infusion 8, and infusion 16.

Note: if infusions 1, 2, 4, 8 or 16 held, the PK and ADA samples should be collected at time of the next PK/ADA timepoint collection.

- Upon treatment completion or discontinuation: end of therapy visit or until the start of a new anti-cancer therapy.

All pre-infusion blood samples should be drawn **within 24 hours** before infusion of pembrolizumab/placebo as described in the Table 6.

Please refer to Table 6 in Section 6.8.3

6.7 Follow-up

6.7.1 In case of early discontinuation prior to first infusion

The following information will be collected:

- Survival status (Refer to Section 6.7.4);
- Disease recurrence assessment: every 12 weeks (± 2 weeks) during the 1st year after randomization starting from the date of enrolment, every 6 months (± 4 weeks window) for the 2nd and 3rd year, and yearly (± 4 week window) for year 4 and 5 . Thereafter the imaging work-up should be performed at least yearly up to year 10. The imaging schedule is based on C1D1 and is not adjusted for delays in treatment. Please refer to Section 7.1.2 for definition of disease recurrence.

6.7.2 Follow-up in the absence of disease recurrence

The reference date for scheduling follow up visits is day 1 of infusion 1

6.7.2.1 Imaging work-up

In the two arms follow up assessment will be performed following the imaging work up schedule.

- every 12 weeks (± 2 weeks) during the 1st year after randomization (starting on day 1 of visit 1),
- every 6 months (± 4 weeks window) during the 2nd and 3rd year

Note: for patients who receive treatment beyond 1 year from randomization, if the last imaging (i.e. during treatment or EoT) is within 4 weeks from the expected first 6 monthly imaging in 2nd year, then the expected first 6 monthly imaging in 2nd year can be omitted.

- yearly (± 4 week window) for year 4 and 5. Thereafter, the imaging work-up should be performed at least yearly up to year 10. The imaging schedule is based on C1D1 and is not adjusted for delays in treatment. The disease recurrence (see Section 7.1.2) will still be collected beyond the 5th year.

Disease status through contrast enhanced chest and upper abdomen CT scan and contrast-enhanced brain CT scan or MRI only if clinically indicated (new evidence of headache or neurologic symptoms);

6.7.2.2 For other tests/investigations/questionnaires

For each follow up visit, the following information/tests will be collected/performed:

- HRQoL evaluation : EORTC QLQ-C30 version 3, EORTC QLQ-LC13 and EQ5D.

Note: questionnaires are filled in every 12 weeks (+/- 3 weeks), during the 1st year after randomization (starting on day 1 of visit 1); every 6 months (+/- 4 weeks) during the 2nd year and then yearly (+/- 4 weeks) until year 5. HRQoL data must be collected regardless of the patient's progression status; no further collection is required beyond the fifth year.

- Thyroid function: tests are performed every 12 weeks (+/- 2 weeks) for the first year of follow-up. In case of elevated TSH, free T3 (or total T3) and free T4 are additionally measured. After the first year of follow-up, thyroid function is evaluated only if clinically indicated.

Note: reference point for TSH collection is determined from the last scheduled protocol imaging. The first Follow-up TSH sample must be collected 12 weeks ± two weeks from the last protocol imaging performed during treatment. If the EOT imaging does not occur in the scheduled imaging interval (every 12 weeks ± two weeks starting from C1 D1), it should not be utilized to calculate the start of the Follow-up visit and TSH collection. Instead, as a reference, it should be taken into consideration the previous image conducted during the treatment period. In addition, TSH collected at the EOT visit is not considered as the first Follow-up TSH.

- Record of further anti-cancer therapies on e-CRF

Note: further anti-cancer therapies should continue to be recorded until withdrawal of consent, death or end of study, which ever occurs first.

- Survival status (Refer to Section 6.7.4)

- Assessment of AEs: if a patient is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last infusion of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible. Serious adverse events will be collected for up to 90 days following discontinuation of treatment or 30 days if the subject initiates new anticancer therapy. Any treatment-related death occurring beyond this time frame must be reported to EORTC.
- If clinically indicated, the following tests/investigations:
  - Physical examination/ECOG performance status see Section 6.2.1;
  - Assessment of any other AEs;
  - Concomitant medication assessment;
  - Hematology and serum chemistry see Section 6.2.2;
  - Urinalysis see Section 6.1.1;

6.7.3 Follow-up after disease recurrence

The reference date for scheduling follow up visits is day 1 of infusion 1

For each follow-up visit, the following tests/exams/questionnaires will be collected/performed:

- HRQoL evaluation : EORTC QLQ-C30 version 3, EORTC QLQ-LC13 and EQ5D.

Note: questionnaires are filled in every 12 weeks (+/- 3 weeks), during the 1st year after randomization; every 6 months (+/- 4 weeks) during the 2nd year and then yearly (+/- 4 weeks) until year 5. **HRQoL data must be collected regardless of the patient's progression status; no further collection is required beyond the fifth year**.

- Thyroid function: tests are performed every 12 weeks (+/- 2 weeks) for the **first** year of follow-up. In case of elevated TSH, free T3 (or total T3) and free T4 are measured. After the first year of follow-up, thyroid function is evaluated only if clinically indicated to continue follow up.

Note: reference point for TSH collection is determined from the last scheduled protocol imaging. The first Follow-up TSH sample must be collected 12 weeks ± two weeks from the last protocol imaging performed during treatment. If the EOT imaging does not occur in the scheduled imaging interval (every 12 weeks ± two weeks starting from C1 D1), it should not be utilized to calculate the start of the Follow-up visit and TSH collection. Instead, as a reference, it should be taken into consideration the previous image conducted during the treatment period. In addition, TSH collected at the EOT visit is not considered as the first Follow-up TSH.

- Record of further anti-cancer treatments;

Note: further anti-cancer therapies should continue to be recorded until withdrawal of consent, death or end of study, which ever occurs first.

- Survival status (Refer to Section 6.7.4)

- Assessment of AEs: if a patient is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last infusion of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible. Serious adverse events will be collected for up to 90 days following discontinuation of treatment or 30 days if the subject initiates new anticancer therapy. Any treatment-related death occurring beyond this time frame must be reported to EORTC.
- If clinically indicated, the following tests/investigations:
  - Physical examination/ECOG performance status see Section 6.2.1;
  - Assessment of any other AEs;
  - Concomitant medication assessment;
  - Hematology and serum chemistry see Section 6.2.2;
  - Urinalysis see Section 6.1.1;

6.7.4 Survival Follow-up

All patients who discontinued study intervention, regardless the reason of discontinuation,

will move into the Survival Follow-up Phase and should be contacted by telephone every 12 weeks (+/- 2 weeks) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Participants should continue the follow-up visits according to the protocol. If the survival follow-up call is scheduled to occur simultaneously with a Follow-up visit, then the call can be omitted.

After year 5, survival follow-up will be conducted every 6 months by telephone.

The reference date for contacting patients for survival follow-up will follow the same schedule as the imaging schedule (Day 1 of infusion 1 (visit 1)).

6.7.4.1 Survival Sweep

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

6.8 Summary tables

6.8.1 Treatment schedule before and during treatment

Table 4. Treatment schedule before and during treatment

	Prior to randomization		**Prior to treatment initiation**		**Treatment Period**			
	Any time after surgery or during adjuvant chemotherapy	Within 12 weeks prior to randomization	Within 10 days prior to treatment initiation	Within 72 hours prior to treatment initiation	Every 3 Weeks (± 3 days)	Every 6 Weeks (±3 days)	Every 12 Weeks (±3 days)	Every 12 Weeks (± 2 Weeks)
Reference Sections	6.2	6.2.1	6.2.2	6.2.3	6.3.1	6.3.2	6.3.3	6.3.4
Registration consent	♦							
Biomedical Research consent	♦							
Main study consent		♦						
Medical history, height, smoking status and demographics		♦						
PD-L1 testing	♦							
Serology HIV, HBV, HCV♣		♦						
Pregnancy test (b-HCG test)[1]				♦	#		#	#
Physical examination (weight, heart rate, BP, T) ECOG PS [2]		♦			♦			
Adverse events		♦			♦			
Conc. Medications		♦			♦			
Hematology [3]			♦		♦			
Serum chemistry [3]			♦		♦			
Urinalysis[5]		♦					♦	
Thyroid function		♦				♦		
12-lead ECG		♦						

	Prior to randomization		**Prior to treatment initiation**		**Treatment Period**			
	Any time after surgery or during adjuvant chemotherapy	Within 12 weeks prior to randomization	Within 10 days prior to treatment initiation	Within 72 hours prior to treatment initiation	Every 3 Weeks (± 3 days)	Every 6 Weeks (±3 days)	Every 12 Weeks (±3 days)	Every 12 Weeks (± 2 Weeks)
Disease evaluation[6]		♦						♦
HRQoL[7]		♦					♦	

♦ in all cases ♣ if clinically indicated according to the local investigator # as per national regulations/institutions guidelines ♠up to 30/90 days for the related AEs/SAEs (see Section 16.6) or if clinically indicated

1. Pregnancy test: serum or urine beta HCG in fertile female study participants. The pregnancy test is to be renewed/repeated during protocol treatment at least monthly or more frequently if required by national regulations/institution guidelines.
2. Physical examination includes ECOG performance status, blood pressure, weight, heart rate, temperature.
3. Complete blood count: WBC, lymphocytes, ANC, monocytes, eosinophils, basophils, RBC, Hgb, Hct, Platelets and serum or plasma chemistry: creatinine, urea or BUN, bilirubin, AST, ALT, alkaline phosphatase, LDH, tot prot, K, Na and Ca, bicarbonate (HCO_3) (HCO_3 testing could be optional in countries where testing is not standard of care), albumin, glucose.
5. Urinalysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed
6. Disease evaluation: chest/upper abdomen CT scan; brain CT and/or MRI if clinically indicated, for example in case of headache or neurologic symptoms. Imaging needs to be based on calendar and not adjusted for delays in treatment. A brain CT scan or MRI must be performed within 12 weeks prior to randomization and only to be done if clinically needed at subsequent imaging visits.
7. HRQoL evaluation : EORTC QLQ-C30 version 3, EORTC QLQ-LC13 and EQ-5D. Questionnaires are filled in every 12 weeks (+/- 3 weeks), during the 1st year after randomization (starting on day 1 cycle 1) and every 6 months (+/- 4 weeks) during the 2nd year. HRQoL data must be collected regardless of the patient's progression status. After year 2 HRQoL will be collected annually (+/- 4 weeks) until the fifth year. See Chapter 10 for more details.

6.8.2 End of Treatment Schedule and Follow up Overview

Table 5. Overview end of treatment and follow up

	End of Treatment	Follow-up		
	4 weeks (± 2 weeks) after last infusion	Discontinuation prior to first infusion	In the absence of disease recurrence	After disease recurrence
Reference Sections	6.4	6.7.1	6.7.2 #	6.7.3 #
Physical examination (weight, heart rate, BP, T) ECOG PS [1]	♦		♣	♣
Adverse events [2]	♦	♠	♠ ♣	♠ ♣
Conc. Medications	♦		♣	♣
Hematology [3]	♦		♣	♣
Serum chemistry	♦		♣	♣
Urinanalysis[4]	♦		♣	♣
Thyroid function	♦		♦[8]	♦[8]
Disease evaluation	♦ [6]		♦[7]	
HRQoL	♦		♦	♦
Survival follow-up[5]		♦	♦	♦
Further anti-cancer therapies			♦	♦
Survival Sweep[9]	♦	♦	♦	♦

♦ in all cases ♣ if clinically indicated according to the local investigator ♠ if the discontinuation was due to an AE

#Follow up assessment will be performed every 12 weeks (± 2 weeks) during the 1st year after randomization , every 6 months (± 4 weeks window) for the 2nd and 3rd year, and yearly (± 4 week window) for year 4 and 5. Thereafter, the imaging work-up should be performed at least yearly up to year 10. The imaging schedule is based on C1D1 and is not adjusted for delays in treatment. Disease recurrence, survival status and further anticancer therapy will continue to be collected beyond the 5th year.

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

2. Assessment of AEs; if at the time of treatment discontinuation, the patient suffers from a severe Grade 3 or 4 AE, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible;

3. Complete blood count: WBC, lymphocytes, ANC, monocytes, eosinophils, basophils, RBC, Hgb, Hct, Platelets and serum or plasma chemistry: creatinine, urea or BUN, bilirubin, AST, ALT, alkaline phosphatase, LDH, tot prot, K, Na and Ca, bicarbonate (HCO3) (HCO3 testing could be optional in countries where testing is not standard of care), albumin, glucose.

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

	End of Treatment	Follow-up		
	4 weeks (± 2 weeks) after last infusion	Discontinuation prior to first infusion	In the absence of disease recurrence	After disease recurrence
5. Survival status: patients to be contacted by telephone approximately every 12 weeks (+/- 2 weeks) If the survival follow-up call is scheduled to occur simultaneously with a Follow-up visit, then the call can be omitted. After year 5, survival follow-up will be conducted every 6 months by telephone (see Section 6.7.4). Upon Sponsor request, participants may be contacted for survival status at any time points during the course of the study. 6 Disease evaluation (see imaging work-up Section 6.3.4): only in case of discontinuation in absence of disease recurrence; 7. Disease status through contrast enhanced chest and upper abdomen CT scan and contrast-enhanced brain CT scan or MRI only if clinically indicated (new evidence of headache or neurologic symptoms) 8 Thyroid function: tests are performed every 12 weeks (+/- 2 weeks) for the first year of follow-up. In case of elevated TSH free T3 (or total T3) and free T4. After the first year of follow-up, if clinically indicated to continue follow up. 9 Can be collected at any time.				

6.8.3 PK/ADA and Translational Research

Table 6. PK/ADA and Translational Research

Samples	Prior to randomization			During treatment						At treatment completion or discontinuation	At tumor relapse
	Step 1	Step 3	Infusion1	Infusion 2	Infusion 4	At week 12	Infusion 8	Infusion 16			
FFPE blocks/slides*	♦										♦[3]
Fresh frozen tissue blocks/slides‡	♦[3]										
Whole blood samples (germline source) (20 mL)†	♦										
Serum samples (10 mL)†						♦[2]				♦[2]	
Serum samples (20 mL)†	♦	♦[1]									♦[2]
PBMC‡		♦				♦[2]					♦[2]
Whole Blood for correlative study (DNA)†		♦									
Whole Blood for correlative study (RNA)†		♦				♦				♦	

Samples	Prior to randomization			During treatment						At treatment completion or discontinuation	At tumor relapse
	Step 1	Step 3	Infusion1	Infusion 2	Infusion 4	At week 12	Infusion 8	Infusion 16			
PK samples[4] (3.5 mL each)**			♦	♦	♦		♦	♦		♦	
ADA samples[4] (6 mL each)**			♦	♦	♦		♦	♦		♦	

1. only if adjuvant chemotherapy was delivered

2. Samples at wk 12, at completion or discontinuation of treatment as well at progression can be collected in a +/- 7 days interval.

3. only if available

4. Pre- infusion trough PK and ADA samples should be drawn before infusion of pembrolizumab/placebo at infusions 1, 2, 4, 8, and 16; at treatment completion/ discontinuation (end of therapy visit(or until the start of a new anti-cancer therapy). All pre- infusion blood samples should be drawn within 24 hours before infusion of pembrolizumab/placebo

*Sample(s) is (are) collected for PD-L1 status analysis following the registration consent, and will be transferred to central biobanks if patient's consent for biomedical research

**Samples are collected following patient's consent for the main study

†Samples are collected following patient's consent for biomedical research

‡Samples are collected following patient's consent for biomedical research and in selected sites

7 Criteria of evaluation

7.1 Evaluation of efficacy

The following paragraphs are a reference to the RECIST version 1.1. The complete criteria are included in the published RECIST version 1.1 document [Ref. 71] also available at http://www.eortc.be/RECIST.

7.1.1 Assessment of tumor lesions

7.1.1.1 Methods of assessment

The determination of patient's eligibility and the determination of tumor progression will be done by local principal investigator based on the schedule outlined for disease evaluation in Table 4. Imaging needs to be based on calendar and not adjusted for delays in treatment. The images will be collected by the central vendor for quality assurance and future central review. The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. The same method of assessment and the same technique should be used to identify and report lesion 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. At the time of occurrence of a lesion, their actual measurements should be recorded on the CRF even when very small (e.g. 2 mm). 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".

- **CT or MRI** are mandatory to establish recurrence. Conventional CT with i.v. contrast with contiguous cuts of 10 mm or less slice thickness is the best currently available and reproducible method to assess and measure lesions. If CT IV contrast is contraindicated, a non-contrast CT is recommended over MRI for radiographic evaluation of the chest. MRI is also acceptable in certain situations (e.g. for body scans). If a patient cannot have a CT scan or MRI with contrast during the screening phase, the patient is not eligible. A CT scan or MRI without contrast is acceptable during the treatment and follow-up phases if the patient develops a medical problem that precludes the use of contrast agents. Performance of a non-contrast CT scan or MRI will be reported as a deviation to the protocol during medical review.
- **PET** alone will not be considered for the disease assessment. Complementary CT/MRI or biopsy must be performed in such cases.
- **Cytology or Histology** are mandatory to confirm recurrence in solitary or in doubtful lesions. Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases.
- **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.

7.1.1.2 Frequency of tumor re-evaluation

The baseline disease evaluation by tumor imaging as outlined in Table 4 should be performed within 12 weeks prior to randomization date. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 12 weeks prior to the randomization date.

Evaluation for tumor recurrence will be performed through contrast-enhanced chest and upper abdomen CT scan to be performed every 12 weeks (+/- 2 weeks) during the 1st year after randomization, every 6 months (+/- 4 weeks) for the 2nd and 3rd year, yearly (+/- 4 weeks) for year 4 and 5. Thereafter, the imaging work-up should be performed at least yearly up to year 10. The imaging schedule takes as reference the start date of treatment (C1D1) and is not adjusted for delays in treatment. Imaging needs to be based on calendar and not adjusted for delays in treatment.

7.1.1.3 Date of recurrence

This is defined as the first day when the RECIST version 1.1 criteria for disease recurrence are met.

The first date when recurrence was observed is taken into account regardless of 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 the date of recurrence.

7.1.2 Disease free survival (DFS)

Definition of date of disease recurrence is given above (see Section 7.1.1.3). Recurrence of disease can be a loco-regional recurrence, a distant (metastatic) recurrence or a second primary. NSCLC and second malignancies will be considered to be events.

Disease Free Survival (DFS) is calculated as the time from randomization to either the date of disease recurrence or the date of death (whatever the cause). The date of first documented disease recurrence (if applicable) will be used as the date of event. Patients alive with no evidence of disease recurrence at the time of their last visit are censored at the time of the last examination.

7.1.3 Overall survival (OS)

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.

7.1.4 Lung Cancer Specific Survival (LCSS)

Lung Cancer Specific Survival (LCSS) is calculated as the time from randomization to the date of death (due to lung cancer specifically). The follow-up of patients still alive will be censored at the moment of last visit/contact. Patients who die from causes other than lung cancer are censored at the time of death.

7.2 Evaluation of safety

7.2.1 Adverse events

All adverse events will be recorded as specified below in the protocol; 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 4.03, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page https://www.eortc.be/services/doc/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 4.03.

Non hematological acute side effects will be assessed and reported separately for each study medication administration, and graded according to the CTCAE version 4.03.

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

7.2.3 Serious adverse events

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 I.

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as a serious adverse events at least with reasonable possibility to be related to study treatment). The cause of death must be reported as "toxicity" and as a serious adverse event. 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

8.1.1 Sample size considerations

The primary endpoints are disease free survival (DFS) in all patients and in a subgroup of patients with **PD-L1 strong positive (tumor proportion score (TPS) ≥ 50%).** CCI [redacted]

Assumptions for the sample size calculation:

CCI [redacted] The study is designed with primary/dual-primary endpoints: DFS in the whole population and DFS in the PD-L1 strong positive sub-population. Assumptions and the testing strategy are given below.

- Overall, an improvement of 14 months in median DFS (from 42 months to 56 months) or equivalent to HR = 0.75 is aimed for the whole population. CCI [redacted]
- [redacted]
- [redacted] The enrollment duration is 52 months with the accrual rates provided in Table 7 below.
- The yearly drop-out rate is 2.5% and 1% for DFS and OS, respectively.

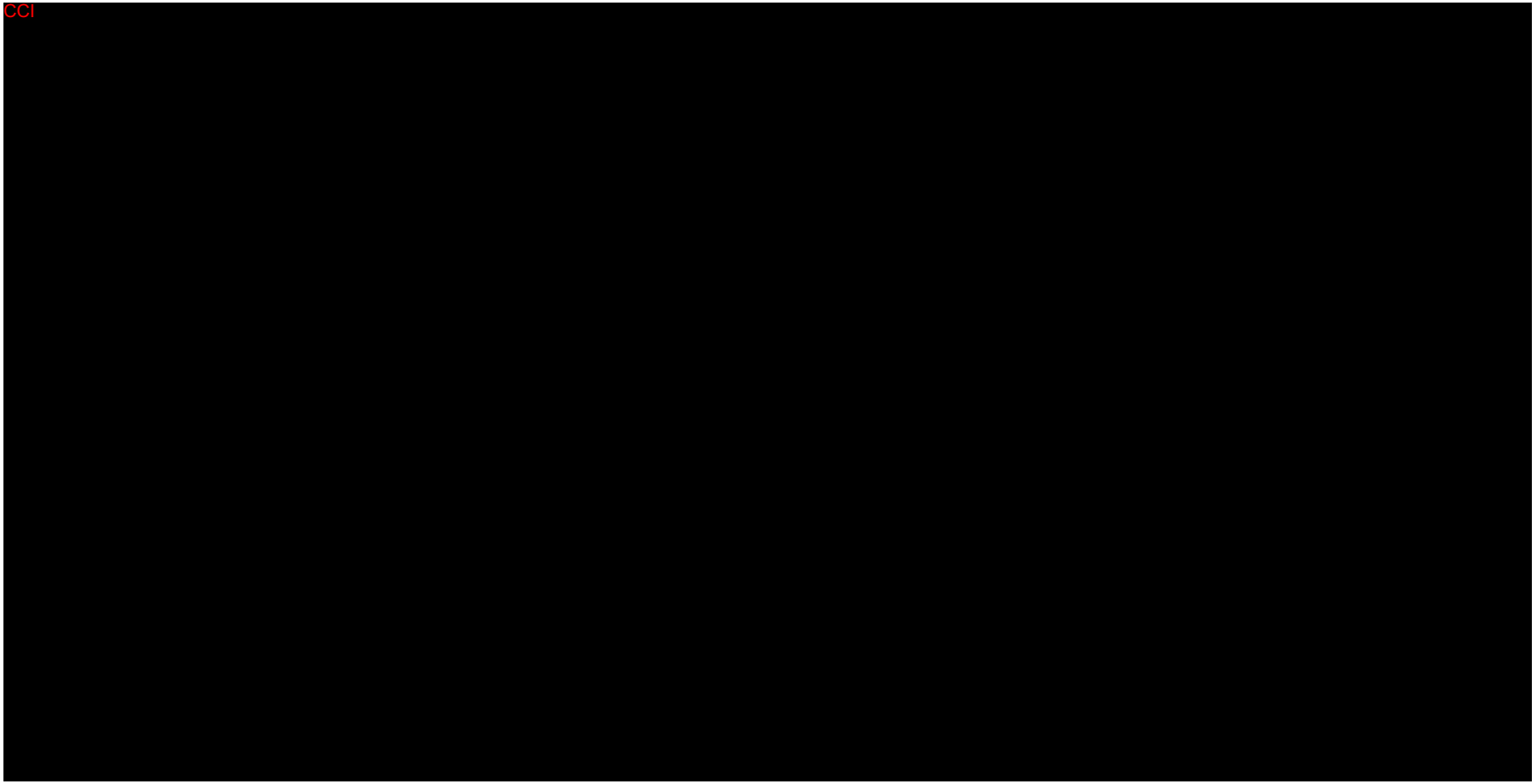
Table 7. Enrollment Pattern

Period	Starting at time	Calendar Time	Accrual Rate
1	0	January 2016	8.375
2	8	September 2016	18
3	26	March 2018	34.24
4	47	December 2019	13.992

- The family-wise error rate (Type I error) for DFS and OS hypotheses is strongly controlled at 2.5%, one-sided. The study uses the graphical method of Maurer and Bretz [Ref. 75] to provide strong multiplicity control for multiple hypotheses as well as interim efficacy analyses. See Figure 3 for an overview of the multiplicity strategy.
- CCI [redacted] The schedule and type of analyses for DFS and OS are given in Table 8 and Table 9, respectively.

- A Hwang-Shih-DeCani (HSD) spending function with gamma = -4 is used to establish the boundary (nominal alpha) in interim and final analysis of DFS and OS for the test of each population. The threshold alphas and HRs for each analysis can be found in Table 8 and Table 9.
- All DFS analyses are DFS event-driven. The timing for interim analysis 1 and 2 will be determined by the number of DFS events in the PD-L1 strong positive population, CCI [redacted]
- CCI [redacted]

Approximately 1180 participants will be randomized in a 1:1 ratio into the experimental arm and the control arm. CCI [redacted] If either of the tests for the primary endpoints is significant, then the study can be declared successful in the respective population.Table 8 and Table 9 summarize the power to reject the null hypotheses for DFS and OS and their corresponding individual hypotheses at the different times of analyses.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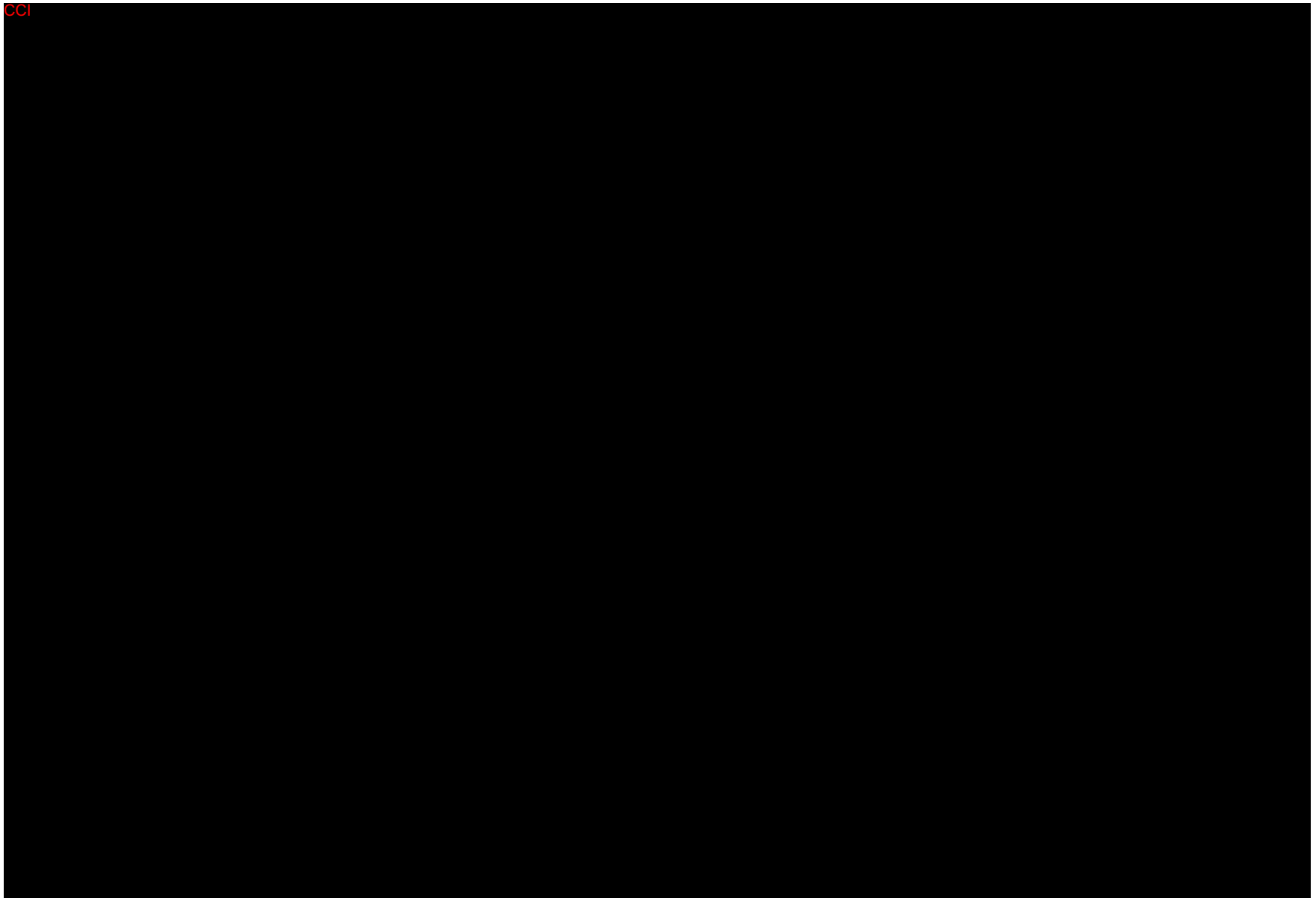
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[redacted]

8.1.2 Randomization and stratifications

All patients entered will be centrally registered at the EORTC Headquarters (for practical details, see Chapter on randomization procedure). The Pocock and Simon Minimization with Biased-coin Assignment methodology [Ref. 73] will be utilized to perform subject randomization for this study. Per suggestion of the ICH E9 statistical guidelines, the algorithm has been modified to incorporate a random allocation component in order to ensure 15% of completely random assignments. Stratification factors are: stage (IB vs II vs IIIA), adjuvant chemotherapy (no adjuvant chemotherapy versus adjuvant chemotherapy), PD-L1 status: negative (TPS=0%) versus weak positive (TPS = 1-49%) - versus strong positive (TPS≥50%) and regions (Western Europe versus Eastern Europe versus Rest of the world versus Asia). Minimization algorithm separately applied for each PD-L1 status, to ensure an optimal balance of treatment arms within each PD-L1 level.

Treatment allocation will be blinded (see Chapter 14).

Note: Tumor staging is based on TNM stage (according to the 7th edition of the TNM classification for lung cancer).

8.2 Statistical analysis plan

8.2.1 Primary/dual-primary and secondary endpoints

The primary/dual-primary endpoints and all secondary endpoints are defined in Chapter 7. Technical derivation of these endpoints using the case report forms(CRFs) is included in Appendix N.

8.2.2 Analysis populations

- Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization.
- Safety population: All patients who have started their allocated treatment (at least one infusion of the study drug(s))

These populations are also applicable to the predefined PD-L1 subgroups.

8.2.3 Statistical methods

8.2.3.1 Efficacy endpoints

The primary analyses of the primary and secondary efficacy endpoints (DFS, OS and LCSS) will be performed on all randomized patients according to the intention to treat (ITT) principle.

Estimates and confidence intervals

Estimates of the median DFS,OS and LCSS will be obtained by the Kaplan Meier technique. The 95% confidence interval (CI) for the median will be calculated using the reflected CI method.

Estimates of the event-free rate at a fixed time point will be obtained using the Kaplan Meier technique and 95% CI will be calculated by the Greenwood's formula for standard deviation. Estimates of hazard ratios and their 95% CI will be obtained by Cox regression. Kaplan Meier curves will be drawn for both the experimental and control arms on the same plot.

Inference

The DFS and OS will be analyzed by a Cox Proportional Hazard Regression with treatment adjusted by the following covariates: stratification factors including stage, PD-L1 IHC expression, adjuvant chemo, regions, and additional factors including histology and smoking status. Permutation test [Ref. 74] will be used as a primary test for DFS to compare the experimental versus the control arm . The Wald test without permutation of allocation sequence will be used as a supportive analysis for DFS, but as a primary test for OS. The hazard ratios and corresponding 95% CIs will be estimated using the multivariate Cox regression model stated above (using Efron's tie-handling method). A sensitivity analysis will include sex (male vs. female) and age (<65 vs. ≥ 65 years) as additional adjustment factors in the Cox regression model. A logrank test with no adjustment factors to compare the two arms will also be performed as a sensitivity analysis.

If a randomized patient is not disease free at baseline, the date of randomization will be used as the date of event for the primary DFS analysis in the PD-L1 strong positive, PD-L1 positive and the whole population.

Analysis of LCSS will be based on the log-rank test and Cox regression model. Competing risks approaches such as cumulative incidence function (CIF), Gray's test, Fine-Gray subdistribution hazard model, etc., will also be performed, where deaths from other causes are considered as competing risks. As no Type I error control is applied to LCSS, the p-values for LCSS analyses, if provided, are nominal only and for descriptive purpose.

Table 10. Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Primary/dual-primary Endpoints				
DFS	P	Permutation test with multivariate Cox regression model§	ITT ♦ all patients, ♦ PD-L1 strong positive ♦ PD-L1 positive	Model-based
	S	Wald test in multivariate Cox regression model Non-adjusted logrank test	ITT ♦ all patients, ♦ PD-L1 strong positive ♦ PD-L1 positive	Model-based
Secondary Endpoints				
OS	P	Wald test in Multivariate Cox regression model	ITT ♦ all patients, ♦ PD-L1 strong positive ♦ PD-L1 positive	Model-based
LCSS	P	Non-adjusted logrank test	ITT ♦ all patients,	Model-based

† P=Primary approach; S=Secondary approach.

‡ Statistical models are described in further detail below:

§ Adjusted by Stage (IB versus II versus IIIA), PD-L1 IHC expression (0 versus 1-49% versus ≥ 50%), Adjuvant Chemo (No chemotherapy vs. adjuvant platinum-based chemotherapy), Histology (squamous vs. non-squamous), smoking status (smokers vs. non-smokers), and regions (Western Europe versus Eastern Europe versus Rest of the world versus Asia).

The strategy to address multiplicity issues with regard to multiple endpoints and interim analyses is described in Section 8.3, Interim Analyses and in the below subsection on Multiplicity.

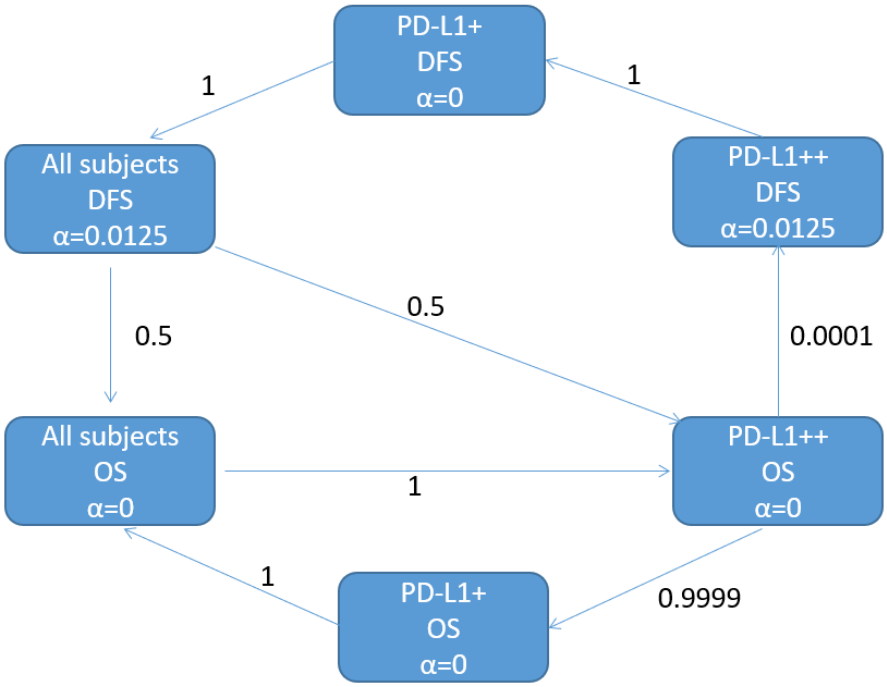
8.2.3.2 Toxicity

Analysis for toxicity is based on the safety population. The worst grade of toxicity/adverse events observed over the whole treatment period according to CTCAE version 4.03 will be displayed. In the primary analysis, no formal statistical analysis will be performed to compare toxicity between arms.

8.2.3.3 Multiplicity

The family-wise error rate (Type I error) for DFS and OS hypotheses is strongly controlled at 2.5%, one-sided. The study uses the graphical method of Maurer and Bretz [Ref. 75] to provide strong multiplicity control for multiple hypotheses as well as interim efficacy analyses. See Figure 3 for an overview of the multiplicity strategy.

Figure 3: Multiplicity Graph for Alpha Re-allocation Strategy



Bonferroni adjustment is adopted, by initially splitting alpha equally to test DFS, i.e. 1-sided alpha = 1.25% is allocated to the whole population and 1-sided alpha = 1.25% is allocated to the PD-L1 strong positive. The graphical method is then applied to determine the multiple testing procedures. If the null hypothesis of DFS is rejected in PD-L1 strong positive subgroup, its alpha is fully reallocated to DFS hypothesis testing in PD-L1 positive subgroup. DFS in the whole population can be tested at alpha = 2.5% when DFS hypotheses in PD-L1 strong positive and PD-L1 positive subgroups are both rejected. OS hypothesis testing in the

whole population and PD-L1 strong positive will not occur until DFS hypothesis is rejected in the whole population. Below is an illustration of possible overall alpha levels for each DFS hypothesis may be tested at.

- DFS in PD-L1++: alpha=1.25% (initial alpha assigned), or alpha=2.5% (once all three OS hypotheses are rejected).
- DFS in PD-L1+: alpha=1.25% (once DFS in PD-L1++ is rejected and OS in PD-L1++ is not rejected), or alpha=2.5% (once all other hypotheses are rejected)
- DFS in the whole population: alpha=1.25% (initial alpha assigned), or alpha=2.5% (if all other two DFS hypotheses are rejected).

Note that a Hwang-Shih-DeCani (HSD) spending function with gamma = -4, determines the boundary of alpha threshold at each IAs for DFS and OS.

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The threshold alphas with the expected number of events are illustrated in Table 8 and Table 9.

In case only one of the primary DFS hypotheses is significant at the time of IAs, then the significant result will be declared in the corresponding population or subgroup. The other primary DFS hypothesis will continuously be tested according to the maturity of the next test, by using the available nominal alpha.

In case all primary DFS hypotheses are significant at the time of IAs, then the significant results will be declared in all the respective populations. In such situation, the study will declare success in all primary hypotheses, yet the analyses for secondary endpoint will be continued as scheduled.

The above multiplicity control strategy is based on current understanding on the PD-L1 biomarker, and is subject to modification based on emerging external data on the prevalence of PD-L1 biomarkers, or the correlation between PD-L1 statuses and the treatment effect.

8.2.4 Pre-planned sensitivity or exploratory analyses

In addition to the analyses mentioned in the previous section, the following sensitivity analyses may also be performed:

- using the ITT population, but considering the stratification factor - Stage (AJCC V7) information as indicated on the CRFs based on pathology report(s). Stage information based on AJCC V8 converted from AJCC V7 and additional information collected in the database may also be considered.
- For the randomized patient not disease-free at baseline, the date of randomization is used as the censoring date for DFS analysis.

- Proportional hazard assumption will be checked. If the data clearly do not follow proportional hazards, medical explanations should be identified and alternative statistical methods will be explored.
- Sensitivity analyses for DFS may also be conducted, adjusted by complete resection status (complete resection vs. uncertain) as assessed and described by the quality assurance for surgery [Ref. 86].

Subgroup analyses are planned to compare DFS by treatment arm in the stratification factors. In addition, subgroup analyses by histology, smoking status, sex and age are also planned. Two cut-off values for age (70 years and 75 years) to define elderly population will be explored to assess the impact of geriatric domains on study primary/dual-primary endpoints and PD-L1 status. Subgroup analyses by complete resection status (complete resection vs. uncertain) as assessed and described by the quality assurance for surgery [Ref. 86] may also be conducted.

The above analyses will be repeated for the secondary endpoint OS.

Exploratory analysis: factors related to the cure rate

Cure rate, defined as proportion of patients who are still alive when the OS curve reaches plateau- will be explored. Any conclusion on cure rate should incorporate all subgroups (mature and less mature observations with respect to the terminal plateau) and consistency check will be performed to examine subgroups with less mature observations if the same conclusion can be drawn for those subgroups.

Proportion of PD-L1 status

Proportion of PD-L1 status: **negative (TPS=0%), weak positive (TPS 1-49%), strong positive (TPS≥ 50%)** will be checked when approximately 100 patients accrued. In case there is any large departure from current assumption of PD-L1 status, necessary statistical adjustment will be considered. If the prevalence of PD-L1 strong positive is lower than expected ,the study design/ sample size may be adjusted based on the observed proportion of PD-L1 strong positive patients to ensure that sufficient number of PD-L1 strong positive patients will be in the study.

Quality of Life

The analyses for Quality of life are defined in Section 10.5.

8.2.5 Prognostic factor analyses

Except for the analyses described in the previous sub-section, there are no other prognostic factor analyses foreseen in the current protocol.

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 visit 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).

DI observed $\left[\frac{mg}{m^2 \times weeks}\right] = \frac{total\ \ dose\ \left[\frac{mg}{m^2}\right]}{total\ \ duration\ [weeks]}$

The relative dose intensity is calculated as the ratio of the dose intensity as calculated above to the dose intensity indicated in the protocol. The dose intensity indicated in the protocol is obtained as the dose specified per visit (in mg/m²).

The dose intensity and the relative dose intensity are presented using median and ranges. The relative dose intensity can also be presented in categories (≤70%, >70-90%, >90-110%, >110-120%, >120.

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

8.3 Interim analyses

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[redacted]

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[redacted]

8.4 End of study

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

1. The overall study ends when the last patient completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up.

2. The trial is mature for the analysis of the primary/dual-primary endpoints as defined in the protocol

3. The database has been fully cleaned and frozen for this analysis

9 Trial Governance and Oversight

9.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The

SAC comprises the scientific experts from EORTC/ETOP as well as the sponsor (MSD) who provide input with respect to trial design, interpretation of trial results and subsequent peer - reviewed scientific publications.

9.2 Trial Steering Committee

This trial will be conducted in consultation with a Trial Steering Committee. The Trial Steering Committee will be chaired by study coordinators from EORTC and ETOP and comprises:

- Study Coordinators from each participating group
- Representative persons from the coordinating group
- Sponsor personnels
- Representative of investigators participating in the trial
- Consulting therapeutic-area experts and clinical trialists

The Trial Steering Committee will provide guidance on the operational aspects of the trial, evaluate recommendations from the Data Monitoring Committee (DMC) and make recommendations to the Executive Oversight Committee (EOC).

Specific details regarding responsibilities and governance of the Trial Steering Committee will be described in a separate charter.

9.3 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive any recommendations made by the Data Monitoring Committee (DMC) and decide upon consultation with the EORTC/ETOP leadership team and the trial steering Committee regarding the trial.

9.4 Data Monitoring Committee

An independent data monitoring committee will be established following EORTC POL-004 "Independent Data Monitoring Committees for EORTC studies" (EORTC IDMC) to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study. Besides its Chair, the EORTC IDMC has a minimum of four (4) permanent members representing each of the following disciplines: medical oncology, radiation oncology, surgical oncology and clinical biostatistics. For interim reviews involving the review of efficacy trial data, the EORTC IDMC will be comprised of all permanent IDMC members and a minimum of three (3) trial specific external members to review the Interim Analysis Report. For interim reviews of safety data only, the EORTC IDMC Chair and at least one of the permanent IDMC members along with a minimum of two (2) trial specific external members will be part of the IDMC.

The IDMC is tasked with making a recommendation to the Sponsor based on their assessment of efficacy and safety information to continue or stop the trial.

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 (Independent Data Monitoring Committee) and approved by EOC.

The membership, key responsibilities of the IDMC, and the corresponding procedures will be defined in an IDMC charter in light of EORTC POL-004.

Safety data are reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators and the Sponsor who will take appropriate measures.

Safety information will be reported to the IDMC, approximately every 6 months unless otherwise agreed upon with the IDMC.Unblinding for global safety reasons and unblinding at interim analysis 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 interim/safety report and will present it to the IDMC.

10 Quality of life assessment

10.1 Rationale

Health related quality of life (HRQoL) is a multidimensional construct, which can be defined as a state of general well being reflecting physical, psychological, and social well being 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.

10.2 Objective

In the present study, HRQoL is a pre-specified exploratory endpoint. The working hypothesis is that pembrolizumab will result in improved DFS compared to placebo with no significant decrement in HRQoL. It is expected that overall self-reported quality of life should be improved due to the improved tumor control but may be affected by immunotherapy related side-effects (fatigue, nausea, pruritus, diarrhea and rash). In addition, the impact of self-reported common symptoms are of interest.

Therefore, overall HRQoL rating and selected symptoms (pain, fatigue, appetite loss, cough, chest pain and dyspnea) will be of interest for the duration of the treatment and for a limited follow-up period afterwards.

10.3 HRQoL instruments

Health related 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. 76]. The average time to complete the questionnaire is approximately 10 minutes.

Additionally, the QLQ-LC13 lung cancer module to the QLQ-C30, which measures HRQoL relevant to specific symptoms (chest pain, cough and dyspnea) common in lung cancer will be included [Ref. 77]. The lung cancer module is meant for use among a wide range of lung cancer patients varying in disease stage and treatment modality. The module comprises 13 questions assessing lung cancer-associated symptoms (cough, haemoptysis, dyspnoea and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. 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 the global health/QoL scale and the pain, fatigue appetite loss, shortness of breath, symptom scales of the QLQ-C30; and the cough, chest pain and dyspnea symptom scales of the QLQ-LC13.

EuroQol (EQ)-5D was developed to assess health outcomes from a wide variety of interventions on a common scale, for purposes of evaluation, allocation and monitoring [Ref. 78]. Index-based values ('utilities') facilitate the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. The EQ-5D-3L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has 3 levels: no problems, some problems, extreme problems. There are more than 100 official language versions of EQ-5D-3L.

English version of these HRQoL Instruments are included as protocol Appendix E, with the list of validated versions available in other languages.

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 E). The pre-treatment questionnaires must be filled in within 12 weeks before randomization. Subsequent questionnaires are filled in every 12 weeks, during the 1st year after randomization; every 6 months during the 2nd year and then yearly until year 5. HRQoL data must be collected regardless of the patient's progression status; no further collection is required beyond the fifth year.

The assessment schedule is chosen to coincide as much as possible with the disease assessment schedule in order to maximize compliance. The week 74 assessment therefore corresponds to the last scheduled on-treatment disease assessment visit at week 48 plus 26 weeks (= 6 months). Subsequent assessments occur at 26 weeks (= 6 months) intervals. Collection beyond year 5 is not deemed necessary as most symptoms will have stabilized by then and the available patient population will have decreased due to attrition.

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. In the event telephone transcript is utilized, the designated study staff should capture the patient's responses on the HRQoL forms. 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 and reviewed twice a year.

10.4.1 HRQoL schedule

The time windows for eligible HRQoL including EQ-5D assessments will be as follows:

Assessment	Time window
Baseline	Can be completed before or on the day of randomization itself but no earlier than 12 weeks before.
Week 12	Can be completed at week 12 (+/-3 weeks) after randomization.
Week 24	Can be completed at week 24 (+/-3 weeks) after randomization.
Week 36	Can be completed at week 36 (+/-3 weeks) after randomization.
Week 48	Can be completed at week 48 (+/-3 weeks) after randomization.
Week 74	Can be completed at week 74 (+/-4 weeks) after randomization.
Week 100	Can be completed at week 100 (+/-4 weeks) after randomization.
Week 152	Can be completed at week 152 (+/-4 weeks) after randomization.
Week 204	Can be completed at week 204 (+/-4 weeks) after randomization.
Week 256	Can be completed at week 256 (+/-4 weeks) after randomization.

⚠ HRQoL data must be collected regardless of the patient's progression status.

10.5 Statistical considerations

The key exploratory HRQoL endpoint relevant for this study is the global health/QoL scale. The following sub-scales and single items will be considered as supportive exploratory HRQoL endpoints: pain, fatigue, appetite loss, shortness of breath, cough, chest pain and dyspnea symptom scales. The other available scales will be classified as "other" exploratory analyses; the financial difficulties scale will not be presented.

The global health/QoL scale will be used as primary outcome of interest for this study. A difference of 10 points on the 100-point QLQ-C30 scale either within a patient or between the two arms will be considered as clinically relevant [Ref. 78]. 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.

Changes in HRQoL scores from baseline per time point will be evaluated by classifying them according to the 10 point change threshold into 3 categories: improved/stable/deteriorated. Patients without a valid HRQoL outcome at a certain time will be considered as having deteriorated at that time. For each patient the proportion of assessments spent in a deteriorated state will be calculated and compared between treatment arms using a non-parametric rank order test in the intent-to-treat population of the whole population and in the PD-L1 strong positive subgroup.

In order to assess the robustness of the results, the following sensitivity analyses will be performed:

- a clinical relevant threshold of 5 and 15 points will be used and patients without a valid HRQoL score will be classified according to the reported reason for non-compliance.
- If adequate compliance available, patients will be classified on valid HRQoL score received after treatment discontinuation only.
- The area-under-the-curve (AUC) will be calculated for each patient based on the global health/QoL scores. Missing values will be considered as 0.
- The change from baseline per time point will be displayed graphically.

These analyses will be repeated on the secondary HRQoL scales.

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. Characteristics of patients with and without valid HRQoL data will be compared and trends over time per dropout pattern will be investigated. Model building will be used in order to investigate whether the compliance mechanism is linked to selected prognostic variables.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the 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.

10.5.2 Other exploratory analyses

The HRQoL scales from the QLQ-C30 and QLQ-LC13 not included as key or supportive exploratory endpoints will be analyzed as "other" exploratory endpoints. The financial difficulties scale will be excluded completely from analysis.

An exploratory analysis of the difference in HRQoL score for progressed patients compared to patients with no radiographic evidence of tumor progression will be subject to compliance and data availability. The aim is to estimate the amount and nature of deterioration in

HRQoL that is associated with disease progression. The change from baseline per HRQoL scale to (i) the most recent HRQoL assessment before progression and (ii) the most recent HRQoL assessment after progression will be calculated and classified based on clinical relevance. A difference of ≥10 points on the 100 point linearly-transformed scale will be considered clinically relevant. Additionally, a longitudinal data analysis model can be constructed, with the HRQoL score as dependent variable, and treatment, time, selected clinical factors, and progression status (time-varying) as independent covariates.

10.6 EQ-5D instrument

The EQ-5D is a general health status and health utility measure [Ref. 64]. 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. 65]. In addition, validated translations for this instrument are available for a number of countries and languages (Appendix E).

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

11 Translational research

PD-L1 IHC expression was described in many histological cancer types, particularly in melanoma and lung cancer. In NSCLC the expression pattern is variable among the different reports ranging from 36 to 50%, according to histologic subtype [Ref. 47, Ref. 48, Ref. 54]. PD-L1 IHC positive tumors showed higher response rates than those with no expression (36 versus 13%) [Ref. 56], with a significant degree of variability according to the testing method as well as positivity definition and threshold used across the various clinical trials.

Data available so far are mainly in the advanced setting but Azuma and colleagues have recently published the results of their study on the PD-L1expression in 164 surgically resected NSCLC. In that series, the expression of PD-L1 was significantly higher for women than for men, for never-smokers than for smokers, and for patients with adenocarcinoma rather than for those with squamous cell carcinoma. The multivariate analysis revealed that the presence of EGFR mutation and adenocarcinoma histology were significantly associated with increased PD-L1 status [Ref. 80]. These data need to be confirmed and prospectively evaluated; heterogeneity in early stage disease needs to be further explored.

PD-L1 status has been correlated with EGFR and RAS mutations and to date the results show no clear trend, largely because of the lack of standardization of the PDL1 definition of positivity, and lack of comparison between antibody use and companion diagnostics.

11.1 Objectives

The aim of this translational part of PEARLS is to explore the immunological parameters that parallel tumor recurrence over time (including new second primaries), in patients treated by pembrolizumab in comparison to the placebo arm. Finally data extracted would help identifying a potential set of prognostic or predictive markers for immune checkpoint inhibitors such as anti PD1 blockers.

Exploratory parameters in this study will be refined according to the current knowledge in the field during trial advancement and at the time of trial completion.

A preliminary proposal of the main objectives of the TR project could focus – based on the current available knowledge in the field and subject to changes accordingly - at least (i.e. not limited to) on analyzing:

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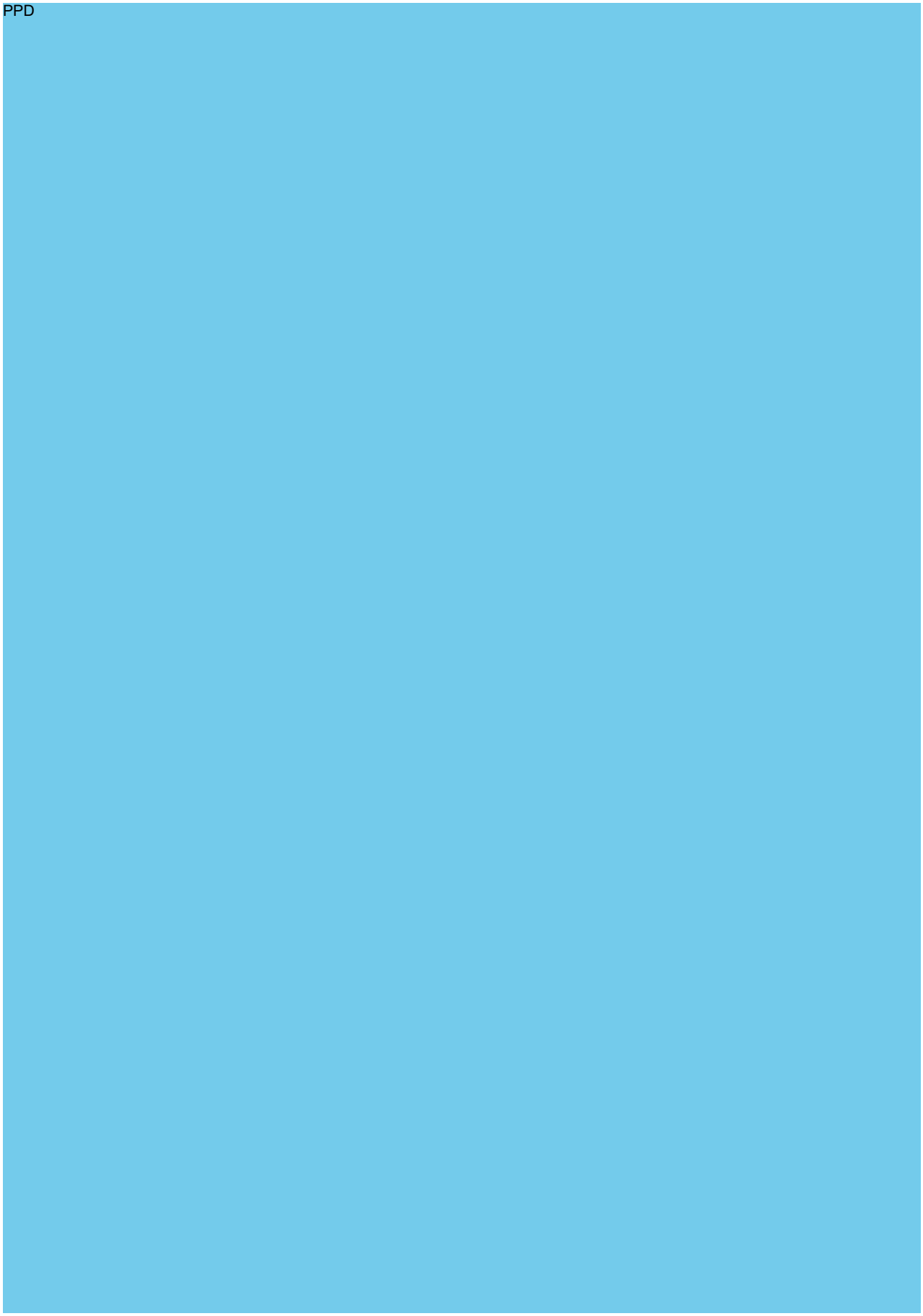
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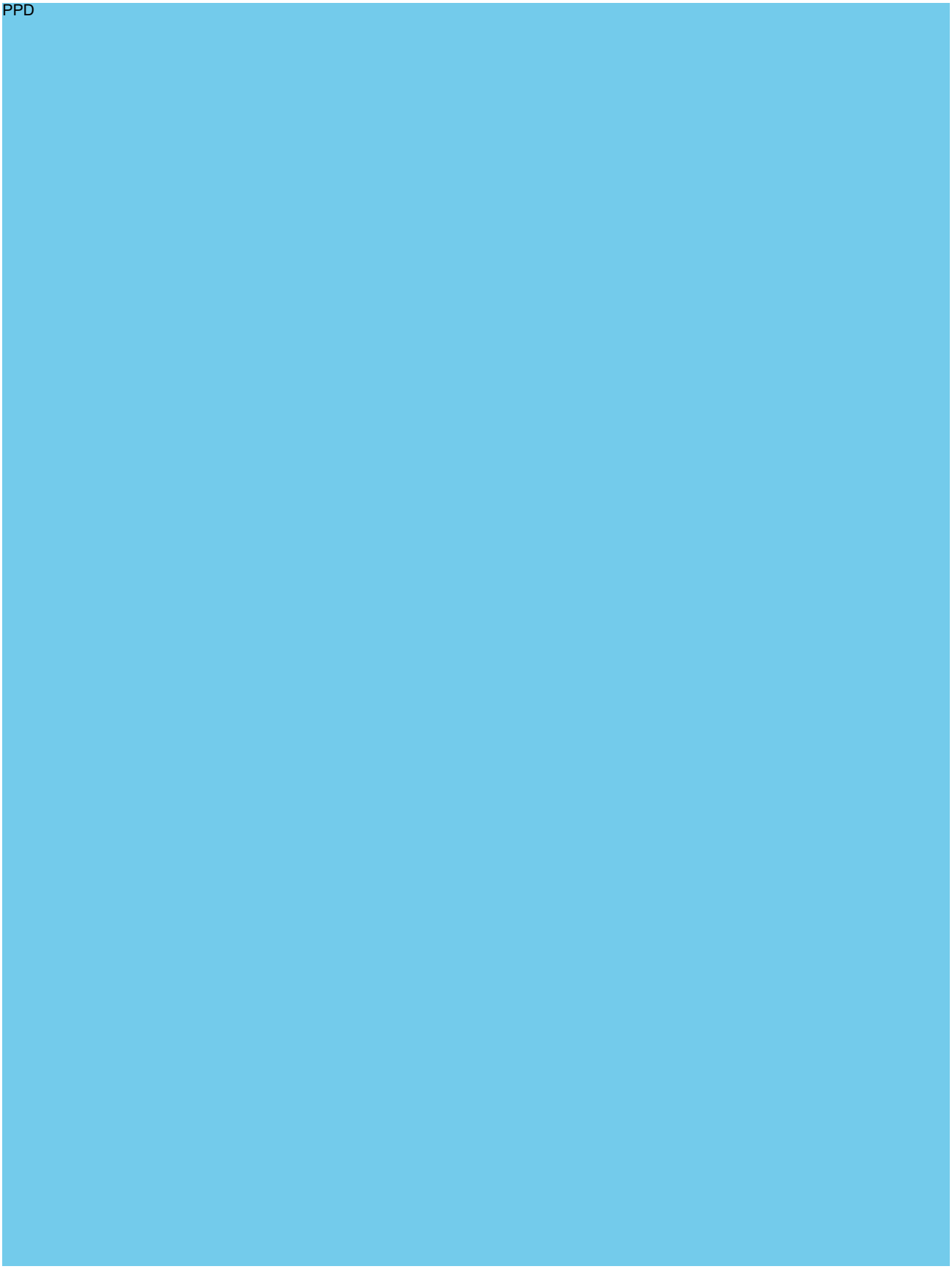
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11.2 Summary of sample collection

This exploratory translational program would require the collection of the following material:

Table 11. Sample collection

Specimen type(s)	Specimen amount	Collection time point(s)	Storage conditions	Estimated sample size
Tumor tissue	FFPE Block (highly preferred) or slides 20-25	At surgery	Blocks: Room temperature (RT) if outdoor temperature is < 24°C/75°F, refrigerarted if RT > 24°C/75°F Slides: refrigerated 2°C-8°C	1180, after central PD-L1 testing for stratification
Tumor tissue	Fresh frozen upon feasibility results for those sites able to collect it (as standard practice) at the time of surgery	At surgery	Fresh frozen: As per local standard practice	Selected centers 50-100 samples randomly distributed between the 2 treatment arms
Tumor tissue	FFPE Block (highly preferred) or slides 20-25	Biopsy at relapse (optional)	Blocks: Room temperature (RT) if outdoor temperature is < 24°C/75°F, refrigerarted if RT > 24°C/75°F Slides: refrigerated 2°C-8°C	Selected patients across all participating centers upon patients consent 150-200 samples
Serum	20 mL	At enrollment step 1	Store at -70°C/-80°C freezer	1180 patients

Specimen type(s)	Specimen amount	Collection time point(s)	Storage conditions	Estimated sample size
Whole blood (germline source)	20mL	At enrollment step 1	Tubes MUST be in -20°C freezer for 24 hrs Transfer to -70°C/-80°C freezer	1180 patients
Serum	20 mL	At enrollment step 3, if adjuvant chemotherapy was delivered only	Store at -70°C/-80°C freezer	Btw 65-80% of the 1180 patients
Serum	10 mL	At week 12 since D 1 infusion 1 – with first CT scan post randomization	Store at -70°C/-80°C freezer	1180 patients
Serum	10 mL	At completion or discontinuation of treatment	Store at -70°C/-80°C freezer	1180 patients
Serum	20 mL	At relapse	Store at -70°C/-80°C freezer	Expected approx. 50% of patients
PBMC	Up to 40 mL	♦ Before treatment start ♦ At week 12 since D 1 infusion 1 ♦ At tumor relapse	Frozen at -70°C/-80°C (max. 21 days) >21 days, store in liquid nitrogen tank. Shipment must be maintained in liquid nitrogen	In selected centers (Switzerland, Spain, France)
Whole Blood for correlative study (DNA)	8.5 mL	Before treatment start (step 3)	Place in -20°C freezer for 24 hrs Transfer to -70°C or colder for at least 24 hrs before shipping	1180 patients

Specimen type(s)	Specimen amount	Collection time point(s)	Storage conditions	Estimated sample size
Whole Blood for correlative study (RNA)	2.5 mL	Before treatment start (step 3) At week 12 since D 1 infusion 1 At completion or discontinuation	Place in -20°C freezer for 24 hrs Transfer to -70°C/-80°C or colder until ready to ship	1180 patients

11.3 Statistical considerations

The primary outcome is tumor recurrence over time (including new second primaries). Tumor and serum samples are collected according to Section 11.2.

The sample size of 1180 patients gives adequate power to detect realistic prognostic effects for immunological parameters on the outcome of interest. More specifically, with 1180 patients available, we will be able to observe 551 tumor recurrences (see also Chapter 8). Assuming that expression of each particular immunological marker will be present in 25-75% of the available sample, the study will be adequately powered (over 80% power) for detecting a targeted HR of 0.78 or less, using a two-sided significance level of 5%. For serial measurements available for about 75% of the total sample of patients, a targeted HR of 0.75 or less can be detected with over 80% power.

Table 12. Maximum detectable HR with around 80% power under different scenarios for the immunological marker incidence.

Marker incidence	Detected HR	alpha	Power
25%	0.78	5%	80%
50%	0.78	5%	80%
75%	0.78	5%	80%
25%	0.75	5%	81%
50%	0.75	5%	81%
75%	0.75	5%	81%

For the analyses exploring the predictive ability of immunological parameters, the critical values will result from procedures to control the false discovery rate (FDR) [Ref. 81, Ref. 82]. When applied to censored failure time outcomes, this approach assumes that censoring is not related to the variables being analyzed. Whether censoring can be considered as random, will be examined during the analysis.

In order to determine the significance of candidate prognostic / predictive markers, we will use Cox model score tests as an initially screening procedure and then apply LASSO as a selection procedure for the markers. Note that we will also evaluate the correlation structure

of the markers. If the correlations are large then we may switch to a procedure more appropriate like the OSCAR [Ref. 83].

A permutation approach [Ref. 82] will be used to control the false discovery rate in the set of variables selected. The initial modeling may only consider the most promising variables based on univariate analyses (all variables will be checked again relative to the final model).

Cross-validated partial likelihood approach (10-fold or 20-fold depending on total sample size) will be used to test the results and the predictability of the derived Cox model. This will be an internal validation of the approach.

11.4 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of sponsor (MSD), collaborating institutions, groups (ETOP) 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 the sponsor or 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.

11.5 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, the FFPE sample will be sent to a central lab for PDL1 expression analysis, the nanostring gene expression profiling and tumor mutational burden. The remaining FFPE tissue and the other biological material from centers will be sent, centralized and stored in a biobank in PPD, where tissue analysis will be performed under the lead of PPD. From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.

The following principles apply to storage of HBM:

- The biobank will have a designated manager responsible for collection and will act as a communication point with the EORTC and ETOP.
- The collected HBM should be documented, i.e. the amount remaining and its location.

- The Study Steering Committee (SSC) will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. This will be done in consultation with the sponsor (MSD). Final decisions on the use of HBM will be determined by a majority vote of the TSC. Additional expertise may be sought through advisory non-SSC members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM 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 the appropriate SSC.
- The SSC will prioritize the TR projects. Access procedures defined by the SSC 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 SSC 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 SSC and the TR project leader(s), as needed.

12 Pharmacokinetic/Pharmacodynamic Evaluations

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart. Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

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.

12.1 Timepoints

Sample collection is currently planned as shown in the Trial Flowchart Section 6.8.3.

12.2 PK Blood Collection for Serum MK-3475

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

12.3 Blood Collection for Anti-Pembrolizumab Antibodies

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

13 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once all 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 the 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 and enroll 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 & randomization procedures

14.1 General procedure

Investigator will register and enroll patients through EORTC, following the standard EORTC procedure. Patient registration and randomization will only be accepted from authorized investigators (see Chapter 13). The randomization through Interactive Voice Response System (IVRS) will occur automatically after the eligibility has been successfully verified.

Patients should be registered directly on the **EORTC online randomization 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 PPD

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 PPD and it is updated annually.

Through internet:	PPD
In case of problems registration by phone:	PPD

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

14.2 Registration (step 1) (ORTA step 1)

A patient can only be registered after signature of the Patient Informed Consent.

A short list of questions needs to be answered during the registration (step 1).

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number: 1416
- 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:

- All eligibility criteria will be checked one by one
- Actual values for the eligibility parameters will be requested when applicable
- date of written informed consent (*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.

14.3 Central confirmation of PD-L1 status testing (step 2)

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

14.4 Randomization (step 3) (ORTA step 2)

Patient randomization will only be accepted after central confirmation (step 2) that a result for PD-L1 status test could be obtained.

A patient can only be randomized after verification of eligibility.

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

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number:1416
- step number: 3
- 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 status 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 (*day/month/year*)

Patient randomization will only be accepted after patient eligibility has been verified.

Patient randomization will be performed automatically in the Interactive Voice Response System (IVRS) .

Additional information and instruction required for patient randomization will be provided in a separate registration & randomization manual.

At the end of the randomization procedure, the treatment will be randomly allocated to the patients (minimization technique) through the IVRS. As this is a triple 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. Description of the blind procedure

IVRS 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.

14.5 Stock management process

The stock of pembrolizumab is maintained in each institution participating in the protocol with the help of IVRS for both ongoing and new patients. The institution needs to confirm to IVRS the reception of each shipment of pembrolizumab before it can be allocated to patients.

14.6 Unblinding procedure

The following are expected authorized unblinding events in the study:

- Emergency Unblinding
- Unblinding by Investigator Request After First Disease Recurrence
- Unblinding at Final Analysis
- Other Unblinding During the Course of the Study

14.6.1 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.

14.6.2 Unblinding by Investigator Request After First Disease Recurrence

The investigator may request authorization for official unblinding of treatment arm upon disease recurrence.

The emergency unblinding methods described in Section 14.6.1 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 for 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.

14.6.3 Unblinding at final analysis

The patient, the investigator and the site team and the EORTC HQ study team will be unblinded only after database lock for the final analysis of the primary endpoint. At unblinding for final analysis, the clinical operations 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.

14.6.4 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 HRQoL form, the EQ-5D questionnaire, the SAE form and the Pregnancy notification form which are paper CRFs.

Copies of the HRQoL forms and the EQ-5D forms should be sent directly to the EORTC Headquarters by one of the following means:

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

SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see Chapter 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"**. The paper CRFs will be made available for downloading through the same website.

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 HRQoLform (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), 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 and EQ-5D: 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.

16 Reporting of Adverse Events, Serious Adverse Events and Other Reportable Safety Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors 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: Selected serious and nonserious AEs are also known as Event of Clinical Interests (ECIs) and must be reported to the Sponsor. Events of clinical interest for this study include:

- 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: Nephritis, Autoimmune nephritis, Renal Failure, Acute Renal Failure, Acute interstitial pneumonitis, Interstitial lung disease, Pneumonitis
- If grade ≥ Grade 2 or any grade resulting in dose modification (please refer to 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 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 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, Hyperglycemia (if associated with ketosis or metabolic acidosis (DKA), 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, Type 1 diabetes mellitus (if new onset), 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 lung cancer is a lung tumor with a different histology from the primary lung tumor; a lung tumor with the same histology as the primary tumor, but occurring > 3 years from removal of the primary tumor and not at the resection margins (local recurrence);

Second primary extra-pulmonary malignancy is a cancer arising in organ other than the lungs; a cancer unrelated to the treatment of a 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 trial 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 v4.03 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 this table:

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

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

All adverse events that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator only 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. For patients that are receiving standard adjuvant chemotherapy during the screening phase; all SARs related to those drugs need to be reported to the Marketing Authorization Holder (MAH) of the administered drug(s).

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), must be reported within 24 hours.

Any SAE/ECI that occurs outside of the SAE detection period (after the 90-days period/initiation of new anticancer therapy) and considered to have a reasonable possibility to be related to the blinded treatment or study participation also needs to be reported to EORTC.

All SAEs must be followed up for outcome.

Signed Patient Registration Informed Consent till randomization:	All SAEs* to EORTC
Randomization till 30 days after last blinded treatment administration:	All AEs
Randomization till 90 days after last blinded treatment administration or 30 days after last blinded treatment administration if subject initiates new anticancer therapy, whichever is earlier:	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
* if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention. SAR related to standard adjuvant chemotherapy during the screening phase need to be reported to MAH of the administered drug(s), NOT EORTC.	

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

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

Reports of pembrolizumab overdose not associated with an adverse event must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event on the study-specific SAE form as an ECI.

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 to:

EORTC Pharmacovigilance Unit:
PPD

Investigators participating through non-EORTC groups should consult their group specific appendix for further details on the reporting of Serious Adverse Events.

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 MSD 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 CRO, the site team and the EORTC HQ study team remain blinded.

The EORTC Pharmacovigilance Unit and MSD 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 Central review of Surgery/Pathology

A retrospective central review of surgery will be organized. Therefore as per local regulations, the surgery and/or histology reports must be available.

17.3 Clinical site monitoring

Clinical site monitoring visits will be performed by the Covance Monitor as described in the study monitoring plan.

17.4 Audits

The EORTC Compliance and Audits regularly conducts audits of EORTC institutions according to the annual audit schedule or based on a risk assessment. In addition, MSD, 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 sub sites, 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 Compliance and Audits 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

https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.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.

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 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 Coordinators work 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 coordinators are responsible for publishing the study results. They will assist the CRP for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinators:

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 Coordinators. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

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

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 Lung Cancer group

Chairman:
PPD

Secretary:
PPD

20 Trial sponsorship and financing

The legal Sponsor of this trial is Merck Sharp & Dohme LLC

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

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 sub investigators 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/sub investigator's responsibility to comply with any such request.

The investigator/sub investigator(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/sub investigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form. The Investigator/sub investigator(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 MSD, is provided in Appendix J - MSD 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, MSD, 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. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD 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 Publication policy

The publication of the main trial results will be written by the Study Coordinators 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 Coordinators, the investigators who have included more than 1.5% of the eligible patients in the trial (by order of inclusion), 2 representatives (statistician and clinical research physician) in charge of the trial at the EORTC Headquarters team and 2 representatives (statistician and clinical research physician) in charge of the trial at ETOP. For publication of translational research results, co-authors will also include scientific collaborators who made substantial contribution to the research.

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

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 groups wish 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.org, or authorized by the Data Monitoring Committee.

The Group Chairmans, the Study Coordinators, the MSD responsible(s) and the EORTC Headquarters team/ETOP 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's (MSD) Executive Oversight Committee (as outlined in Section 9.3) 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 (MSD) at the earliest practicable time for review, not less than 30 days before submission or presentation unless otherwise set forth in the CTA.

Sponsor (MSD) 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

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Appendix B: Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	alkaline phosphatase
ANC	Absolute neutrophil count
AR	Adverse reaction
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	area-under-the-curve
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CRO	Contract Research Organization
CRF	Case Report Form
DILI	Drug Induced Liver Injury
DIC	Disseminated Intravascular Coagulation
DFS	Disease Free Survival
DKA	diabetic ketoacidosis
DNA	Deoxyribonucleic acid
DMC	DMC Data Monitoring Committee
DSUR	Development Safety Update Report
ECI	Event of Clinical Interest
ECI	Epidural Corticosteroid Injection
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EGFR	EGFR: Epidermal Growth Factor Receptor
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
ETOP	European Thoracic Oncology Platform

ESMO	European Society for Medical Oncology
EVCTM	EudraVigilance Clinical Trial Module
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	FFPE: Formalin Fixed Paraffin Embedded
FSH	Follicle-stimulating Hormone
FWER	Family wise error rate
GMP	Good Manufacturing Practice
HBM	Human biological material
HCO_3	Bicarbonate
HIV	Human Immunodeficiency Virus
HLA	Human Lymphocyte Antigen
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
HUS	Haemolytic Uraemic Syndrome
IA	Interim Analysis
IASLC	International Association for the Study of Lung Cancer
ICH/GCP	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use / Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IFN	interferon
IHC	Immunohistochemistry
IL-2	interleukin-2
ILD	interstitial lung disease
irAE	Immune-related Adverse Event
IVRS	Interactive Voice Response System
ITIM	immunoreceptor tyrosine-based inhibition motif
ITP	Idiopathic (or immune) Thrombocytopenia Purpura
ITSM	immunoreceptor tyrosine-based switch motif
ITT	intention to treat

IV	Intravenous
K	Potassium
LACE	Lung Adjuvant Cisplatin Evaluation
LCSS	Lung Cancer Specific Survival
MSD	Merck Sharp & Dohme LLC
MTD	Maximum Tolerated Dose
Na	sodium
NED	No evidence of disease
NGS	next-generation sequencing
NSCLC	Non Small Cell Cancer
ORR	Overall Response Rate
ORTA	Online Randomized Trials Access
OTC	over-the-counter
OS	Overall Survival
PD-1	Programmed Death receptor 1
PD-L1	Programmed Death-Ligand 1
PK	pharmacokinetics
PS	Performance status
QA&C	Quality Assurance and Control Unit
Q2W	every 2 weeks
Q3W	every 3 weeks
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
seqID	sequential patient identification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSC	Study Steering Committee

SUSAR	Suspected Unexpected Serious Adverse Reaction
TAA	tumor-associated antigens
TB	Tuberculosis Bacillus
TILs	tumor infiltrating lymphocytes
TNF	tumor necrosis factor
TPS	Tumor proportion score
TR	Translational Research
TRAC	Translational Research Advisory Committee
TTP	Thrombotic Thrombocytopenic Purpura
UAR	Unexpected Adverse Reaction
ULN	upper limit of normal
VATS	Video-assisted thoracoscopic surgery

Appendix C: ECOG performance status scale

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

Appendix D: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address:**https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40** .

The EORTC Headquarters web site https://www.eortc.be/services/doc/ctc/ provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix E: EORTC Quality of Life evaluation: guidelines for administration of questionnaires - EORTC QLQ-C30 (version 3) - EORTC QLQ-LC13 - EQ-5D – Health Questionnaire

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 questionnaires administered via paper.

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 timepoint when he/she is supposed to complete it.

9. Administration via telephone

If it is deemed not in the best interest of the safety of the patient, the questionnaires may be collected via telephone interview.

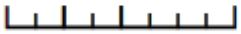
The interviewer must confirm he is speaking to the correct person. The interviewer must identify how many questions there are, what the response options are and what the recall time (e.g. during the past week) is. All questions should be attempted. The interviewer must allow enough time to answer and can can repeat the questions and/or the response options to patients as many times as they request. But the interviewer must not suggest any answers or alter the question.

The interviewer records the answer chosen by the patient. The patient is allowed to skip a question, if he/she requests so. If the patient did not answer all questions, the interviewer must offer the patient the opportunity to read them again.

Thank you very much for your cooperation.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Today's date (Day, Month, Year): 31 

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ-LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4
If yes, where _____	1	2	3	4
43. Did you take any medicine for pain?	1	2	3	4
1 No **2 Yes**	1	2	3	4
If yes, how much did it help?	1	2	3	4

Health Questionnaire

English version for the UK

(Validated for Ireland)

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 ❑

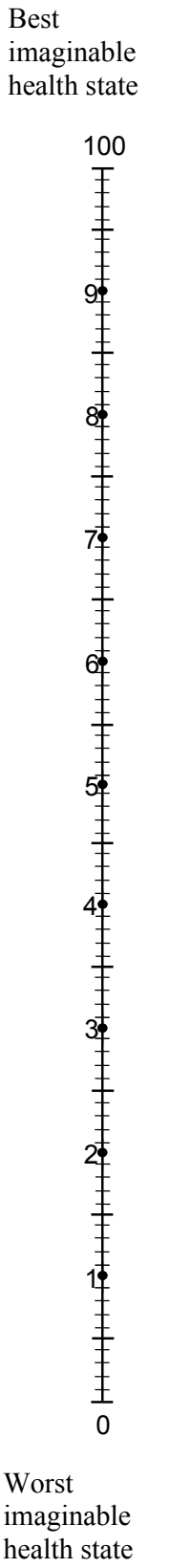
I am moderately anxious or depressed ❑

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 F: IASLC VII TNM staging

Stage groupings

Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

Primary tumor (T)	
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus (i.e., not the main bronchus)
T1a	Tumor ≤2 cm in diameter*
T1b	Tumor >2 cm but ≤3 cm in diameter
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features**:
	Involves main bronchus, ≥2 cm distal to carina
	Invades visceral pleura
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm
T2b	Tumor >5 cm but ≤7 cm

Primary tumor (T)	
T3	Tumor >7 cm or any of the following:
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)
	Atelectasis or obstructive pneumonitis of the entire lung
	Separate tumor nodules in the same lobe
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional lymph nodes (N)	
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion***
M1b	Distant metastasis (in extrathoracic organs)
*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a. **T2 tumors with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cms but no larger than 7 cms. ***Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopical examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.	

Appendix G: Guidelines for management of toxicity

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation as per Table 1 below.

Table 1. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.				
irAEs	Toxicity grade (CTCAE v4.03)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg	• Monitor with liver function tests (consider weekly or more frequently

General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.				
			prednisone or equivalent) followed by taper	until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal
[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal
[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.
[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Patients who have a Grade 2 endocrinopathy, requiring ongoing hormonal replacement therapy, may restart pembrolizumab if treatment interruption was less than 12 weeks.

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). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, but no more than a maximum of 12 weeks for each instance. If the interruption is greater than 12 weeks the PI must discuss continuation in the trial with the Sponsor prior to administering additional therapy. For more info, please refer to Section 6.3.

Appendix H: Supportive care

Subjects 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 infusion 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.

- **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.
- **Diarrhea/Colitis**:

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

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

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:

Thyroid disorders can occur at any time during treatment. Monitor 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 2-4** hypothyroidism):
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

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

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

Table 1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Table 1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (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 participant 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 participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine** Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	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 v4.03 (CTCAE) at http://ctep.cancer.gov		

Appendix I: Event Of Clinical Interest Guidance Document

PEMBROLIZUMAB PROGRAM

(MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 5.0

REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	PPD	Initial Release of guidance document for MK-3475
2	07-June-2013		Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents. Modified Categories for irAEs: Replaced GI with Colitis category. Removed Neurologic category. Added Renal category. Removed detail in the irAE Guidance document that can be located in the Investigator's Brochure for MK-3475. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. Also placed a pull-out quick-review sheet in the Appendix. Updated background, diagnosis and course of treatment details for irAEs.

Version	Effective Date*	Revision Author	Action
3	10-Sep-2014	PPD	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document". Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 Clarified the scope of the document and the reporting window for ECIs Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines Clarified that ECIs must be reported to Merck within 24 hours regardless of attribution to study treatment or etiology. Updated Section 3 For All Sections, removed the Course of Action for Grade 1 events. - Section 3.1 Pneumonitis Moved Pneumonitis to beginning of ECI Section Updated management guidelines for Grade 2 and Grade 3-4 events - Section 3.2 Colitis:

Version	Effective Date*	Revision Author	Action
			Updated AE terms and ECI criteria, updated course of action language for clarity - Section 3.3 Endocrine: Updated ECI criteria and updated course of action language for clarity. Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines. - Section 3.4 Hematologic: New section added. - Section 3.5: Hepatic: Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity - Section 3.6 Neurologic: New section added. - Section 3.7 Ocular: Changed the name of this section from Eye to Ocular Added the term “iritis”, updated ECI guidance, and updated course of action language for clarity - Section 3.8 Renal: Updated section for clarity. - Section 3.9 Skin: Updated list of terms and added terms for reporting of other skin ECIs; added section 3.9.1: Immediate Evaluation for Potential Skin ECIs

Version	Effective Date*	Revision Author	Action
			- Section 3.10 Other: Updated list of terms for clarity; revised course of action for clarity. - Section 3.11 Infusion Reactions: New section added. - Section 3.12: Follow-up to Resolution: New section added. - Section 4: References updated. - Section 5: ECI table updated for consistency with Table 1. - Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added. - Section 7: Appendix 3 – Presentation of the Dermatologic Event: New section added. - Section 8: Appendix 4 – Focused Skin Examination: New section added.

Version	Effective Date*	Revision Author	Action
4	04-Dec-2014	PPD	Table 1 Updated Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE) Section to include: Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA) Created new section in Table 1 – Endocrine (reported as ECI) and added: Type 1 diabetes mellitus (if new onset) Hepatic: Clarified Transaminase elevations as: Transaminase elevations (ALT and/or AST) Section 3.2 Colitis Updated the duration of diarrhea requirments under the Course of Action for Grade 2 and Grade 3 Section 3.3 Endocrine Clarified Course of Action for hyperthyroidism and hypothyroidism Added Course of Action section for Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 hyperglycemia Section 5 Updated Reference Table in Appendix 1
5	18-Dec-2014	PPD	Section 3.3 Endocrine Updated the Course of Action for Hypophysitis Merged Grades 2-4 into one course of action

*Ensure that you are using the most current version of this document.

TABLE OF CONTENTS

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review [1-11], 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 MSD within 24 hours 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 subject data. Table 1 provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 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 1 and reported to MSD 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.

Table 4: Events of Clinical Interest

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	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
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 (ALT and/or AST)
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		

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

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 your local Sponsor contact.

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.

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to MSD within 24 hours regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 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). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

Please refer to the Data Entry Guidelines (DEGs) for your protocol.

Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI).

3. ECI CATEGORIES AND TERMS

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor 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.

Course of Action

Grade 2 events:

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

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.

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 events:

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.

3.2 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 the Sponsor 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.

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 for greater than 3 days, 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

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):

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 events:

Report as ECI

Permanently discontinue pembrolizumab.

Manage as per Grade 3.

3.3 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 the Sponsor 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.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-4 events:

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.

Hyperthyroidism and 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, Grade 2-4 hypothyroidism events:

Report as ECI if appropriate (see Table 1)

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 events:

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 hyperthyroidism events:

Report as ECI

Discontinue pembrolizumab.

Manage as per Grade 3

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)

Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of pre-existing diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

Course of Action

T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:

Report as ECI if appropriate (see Table 1)

Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.

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.

Consultation with an Endocrinologist is recommended.

Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

3.4 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 the Sponsor 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.

Course of Action

Grade 2 events:

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 events:

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.

Grade 4 events:

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

3.5 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 the Sponsor 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.

Course of Action

Grade 2 events:

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.

Grade 3 events:

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 events:

Report as ECI

Permanently discontinue pembrolizumab

Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor 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.

Course of Action

Grade 2 events:

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 events:

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.

3.7 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 the Sponsor 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.

Course of Action

Grade 2 events:

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 events:

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 events:

Evaluation by an ophthalmologist is strongly recommended

Permanently discontinue pembrolizumab.

Treat with corticosteroids as per Grade 3 above

3.8 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.

Course of Action

Grade 2 events:

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 events:

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.

3.9 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.

Course of Action

Grade 2 events:

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 events:

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 events:

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.

3.9.1. 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 subject 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 subject’s study records.

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

B. Past Medical History:

Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:

Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:

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

E. Focused Skin Examination:

Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult

Refer the subject to a dermatologist as soon as possible.

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

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

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

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

3.10 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.

Course of Action

Grade 2 events or Grade 1 events 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 events:

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 events:

Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.

Discontinue pembrolizumab

3.11 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.

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 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.	Subject 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject 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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

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

Clinical course of the event

Course of treatment

Evidence supporting recovery

Follow-up to the clinical course

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

4. REFERENCES

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5. APPENDIX 1 –Events of Clinical Interest (ECI) – Reference Table

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	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
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 (ALT and/or AST)
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		

6. APPENDIX 2 – 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

7. APPENDIX 3 – 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

8. APPENDIX 4 – 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 J: MSD Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki. B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial. 2. Site Selection

MSD’s clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation,

sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts thar are important to patients, physicians, and payers. 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 such as multiplicity.

MSD’s policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Subject Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator’s brochure, and other relevant documents must be reviewed and approved by an IRB/ERC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participants safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participants welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from a MSD 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

MSD is committed to safeguarding subject confidentiality, to the greatest extent possible as well as applicable data protection rights. Unless required by law, only the investigator, sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.D. Genomic Research

Genomic Research will only be conducted in accordance with a protocol and informed consent authorized by an Ethics Committee.IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participants referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD 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. V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.VI. Letters to Patients

At the close of the trial after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product 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 a look-alike [insert tablet/capsule/device/vaccine] created by the Sponsor to resemble the drug/vaccine [insert competitor drug trade name followed by its generic name in parentheses] as much as possible. You may also have received the active drug/vaccine [insert competitor drug trade name followed by its generic name in parentheses] as manufactured by [insert competitor drug manufacturer's name]."

Appendix K: Lobe-Specific Nodal Dissection

Right-sided resection	Left-sided resection
Right Upper Lobe (RUL) Levels 2R, 3a, 4R, 7 Right Middle Lobe (RML) Levels 2R, 3a, 4R, 7 Right Lower Lobe (RLL) Levels 4, 7, 8, 9 RUL & RML Levels 2R, 3a, 4R, 7 RML & RLL Levels 2R, 3a, 4R, 7, 8, 9 RUL & RML & RLL (pneumonectomy) Levels 2R, 3a, 4R, 7, 8, 9	Left Upper Lobe (LUL) Levels 3, 5, 6, 7 Left Lower Lobe (LLL) Levels 7, 8, 9 LUL & LLL (Pneumonectomy) Levels 3, 5, 6, 7, 8, 9
Important Note: Minimum acceptable nodal dissection is level 7 + another lobe specific mediastinal nodal level, which is dependent on the location of the primary lung tumor.	

Appendix L: Barrier Contraception methods

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide, as per local regulations and guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestation al agent (including oral, subcutaneous, intrauterine, or intramuscular agents). 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 parti cipate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. 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.

Appendix M: Recommendation 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 180 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 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor. 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 or more frequently if required by national regulations/institution guidelines.

(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 N: Disease Status and primary/second endpoints derivation

Disease free Survival (DFS), overall survival (OS) and Lung Cancer Specific Survival (LCSS) are the primary and secondary endpoints of this study which is defined in Chapter 7. Below, disease status definition and derivation of endpoints **from the case report forms (CRFs)** is outlined.

1. Disease status

Disease status will be reported in the full ITT population, and entails the tabulation of the following event frequency. The reporting will be repeated in the PD-L1++, PD-L1+ sub-populations.

Events or censoring will be categorized as follows:

1. Recurrence (PD);
2. New secondary malignancy
3. Death
4. Alive with no recurrence nor secondary malignancy.

In addition, for those with recurrence, type of recurrence will be tabulated as follows:

1. Local and or regional
2. Distant metastasis
3. Both Recurrence (PD);

2. Date of recurrence, secondary malignancy or death

The event could be in the following form:

a. First date of recurrence (for DFS)
b. Date of secondary malignancy (for DFS)
c. The date of death (for DFS, OS and LCSS)

2.1 Date of recurrence is recorded in the recurrence form (**formrec**), from variable `dtassrec`. Type of recurrence (1=Local and\or regional/2=Distant metastasis/3=Both) is taken from variable `typrec`.

2.2 Date of secondary malignancy is recorded in follow up form (**formfu**) and end of treatment form (**eotform**). In the follow up form **formfu** (var = DTNEWFU,where NYNEWFU = 1) and in the end of treatment form **eotform** (var= DTNEW, where NYNEW =1)

Apart from the above dates, the following dates need be checked to ensure that the recurrence dates are consistent and captured in the recurrence form in (2.1).

- From the Imaging Assessment form (IMASS), the first date of assessment for which the reported result was abnormal, lung tumor related and either
  - a) pathology was done and positive for lung tumor or
  - b) the method of assessment was CT or MRI

In addition, the following information will be used to check for the recurrence:

- From the Clinical Assessment form (CASS): the first date of visit at which a recurrence since the previous examination was reported.
- The first reported date of recurrence from the Follow-up (FU) form.

2.3 Date of death is taken from end of treatment form, **eotform** (dtssof, ssof=2) or follow up form, **fuform** (dtssfu, ssfu= 2) or survival sweep form **sweepform** (dtsssweep, sssweep = 2)

2.4 Date of last disease evaluation is taken from the following:

- \- Date of randomization
- \- IMASS form, **imassform**(dtmethod1,dtmethod2,dtmethod3, maximum).

In each patient without DFS event, the max of those dates will be used as date of censoring.

2.5 Date of last known to be alive is taken from the last dates of the following forms (dates):

- Date of last disease evaluation as in (**2.4**)
- **formFAT** (dtsurfat, dtrtfat, dtst1fat, dtst2fat, dtst3fat, dtst4fat, dtst5fat, dtst6fat, dtst7fat, dtsp1fat, dtsp2fat, dtsp3fat, dtsp4fat, dtsp5fat, dtsp6fat, dtsp7fat)
- **formEOT** (dtssof, dtnew)
- **formLBBIO** (dtbio and nybio = 1)
- **formLBHEM** (dthem and nyhem = 1)
- **formLBTHY** (dtthy and nythy = 1)
- **formLBURI** (dtLBURI and nyLBURI = 1)
- **formTRT** (dttrt and nytrtadm=1)
- **formSWEEP** (dtsssweep and sssweep in (1,2))
- **formFU (**dtssfu**)**
- **formAE** (aestdtc, aeendtc)

In each patient without OS event, the max of the above dates will be used as date of censoring.

2.6 Date of death due to NSCLC is taken from end of treatment form, **eotform** (dtssof, ssof=2 and rdeadof =1) or follow up form, **fuform** (dtssfu, ssfu= 2 and rdeadfu =1) or survival sweep form **sweepform** (dtsssweep, sssweep = 2 and) when cause of death is PD (**eotform** [dtssof, ssof=2] or **fuform** [dtssfu, ssfu= 2]). If cause of death is missing, not defined or not available then such case will be treated as censoring at the date of death.

3. Disease free survival endpoint

Disease free survival considering the following event or censoring:

- Date of recurrence (**2.1**)
- Date of secondary malignancy (**2.2**)
- Date of death (**2.3**)
- Censoring: In the absence of event, date of last disease evaluation (2.4).

Disease Free Survival (DFS) is calculated as the time from randomization to either the date of disease recurrence or the date of death (whatever the cause). Patients alive with no evidence of disease recurrence at the time of their last visit are censored at the time of the last examination.

Therefore, DFS is the time between the date of randomization and the earliest date among of events or censoring as described in **2.1, 2.2, 2.3** and **2.4**.

Note that in some rare occasions, patients are randomized but are found to be not disease free later on. Such cases are detected in the CRF by checking the recurrence dates prior to randomization. Such cases are handled as follows: the date of randomization is used as the recurrence time or censoring in the analysis (see Section 8.2.3).

4. Overall survival endpoint

This endpoint considers the following as events:

- Death (**2.3**)

The endpoint is calculated as the time duration from randomization until the date of death (**2.3**), if the patient died. If the patient does not experience an event, he/she will be censored at the last follow-up date (**2.5**).

5. Lung Cancer Specific Survival endpoint

This endpoint considers the following as events:

- Death due to NSCLC (**2.6**)

This endpoint is calculated as the time duration from randomization until the date of death due to NSCLC (**2.6**), if the patient died. If the patient died from other causes than NSCLC (event in **2.3** but not in **2.6**) then the patients will recorded as censoring (for the primary analysis) or competing event (for the supporting analysis, competing risk). If the patient does not experience either event or competing event, he/she will be censored at the last follow-up date (2.5). This latter will be analysed with competing risk method.