SPONSOR: **NKI/AVL**

TITLE: **Randomized Phase II, 2-arm study of Pembrolizumab after high dose radiation (SBRT) versus Pembrolizumab alone in patients with advanced non-small cell lung cancer.**
Acronym: PEMBRO-RT study

EudraCT NUMBER: **2014-005118-49**

Date: **December 11th, 2017**
Version: **11.0**

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
CBC	complete blood count
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRF	case report form
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTV	clinical tumor volume
DCR	disease control rate
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	eastern cooperative oncology group
EGFR	epithelial growth factor receptor
ERC	exempt review committee
FDA	food and drug administration
FDAAA	food and drug administration amendments act
FDAMA	food and drug administration modernization act
GCP	good clinical practice
GFR	glomerular infiltration rate
GTV	gross tumor volume
Gy	gray
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
IMRT	intensity modulated radiotherapy
IND	investigational compound number
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
irECI	immune-related event of clinical interest
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif

IV	intra venous
LDH	lactate dehydrogenase
MDSC	myeloid-derived suppressor cells
MEL	melanoma
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	national cancer institute
NK	natural killer
NSAID	non-steroid anti-inflammatory drug
NSCLC	non small cell lung cancer
NKI	netherlands cancer institute
OAR	organ at risk
OS	overall survival
OTC	over-the-counter
PFS	progression free survival
PMDA	pharmaceutical and medical devices agency
PD	pharmacodynamic
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PK	pharmacokinetic
PT	prothrombin time
PTV	planning tumor volume
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
RR	response rate
RT	radiotherapy
SAE	serious adverse event
SBRT	stereotactic body radiation therapy
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TILs	tumor-infiltrating lymphocytes
Tregs	T regulator cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VMAT	volumetric modulated arc therapy
WBC	whole blood count

1.0 TRIAL SUMMARY

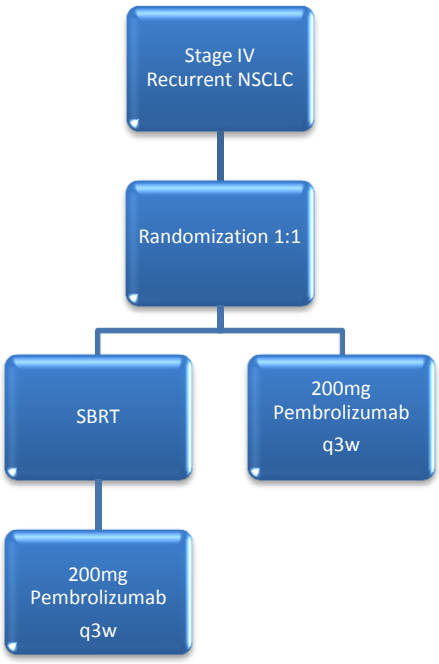
Abbreviated Title and rationale	PEMBRO-RT To investigate the effects of pembrolizumab, a PD-1 inhibitor, with or without SBRT in patients with recurrent NSCLC
Objective:	To determine the Overall Response Rate (ORR) at 12 weeks. Secondary endpoints include safety as determined by adverse events, disease control rate (DCR) at 12 weeks, progression free survival (PFS), overall survival (OS) as determined by immune-related Response Criteria (irRC). Exploratory endpoints include the (immune) effects on tissue samples after exposure to pembrolizumab at 6 weeks
Trial Phase	Phase 2
Trial Type	Randomized study
Route of administration	I.V.
Trial Blinding	No
Treatment Groups	Two experimental groups
Number of trial subjects	74
Estimated duration of trial	18 months
Duration of Participation	30 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open label, three center, randomized 2-arm phase II study comparing pembrolizumab treatment alone with pembrolizumab after SBRT.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To observe an increase in Overall Response Rate (ORR) from 20% in the pembrolizumab alone arm to 50% in the pembrolizumab after SBRT arm at 12 weeks.

(2) **Hypothesis:** In a significant subset of patients with recurrent NSCLC immunotherapy after SBRT will be superior to treatment with immunotherapy alone. SBRT, given to a single metastatic site of the tumor, will augment the immune response to the tumor.

3.2 Secondary Objectives & Hypothesizes

(1) **Objective**:

- Disease Control Rate (DCR), defined as the percentage of patients having a complete response, partial response or stable disease at 12 weeks,
- PFS, defined as time from randomization to disease progression or death,
- OS, defined as time from randomization to death (of any cause).
- Toxicity

3.3 Exploratory Objective

(1) **Objective:** Paired tumor material and blood samples will be used to identify possible new biomarkers for selection of patients who might benefit from immunotherapy. Tumor

tissue will be examined for at least the expression of the following: PD-L1 expression (DAKO kit); PD1 expression; Tregs; NK infiltration; CD3+, CD8+ CD45RO T cells, and M2 macrophages.
Fluid Phase Biopsies (peripheral blood) will be collected for further analysis and comparative studies.

(2) **Hypothesis**: The addition of SBRT before the start of immunotherapy treatment will result in an increase in infiltration of Cytotoxic T lymphocytes and enhanced anti-tumor immune response.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene PDCD1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. 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 [13; 14]. PD-1 was shown to be expressed by activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or

can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18; 19; 20; 21]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-L1 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [18]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [22]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Despite the availability of accepted second line chemotherapy agents, patients with recurrent NSCLC will still progress quickly; have significant side effects and die of the disease. Therefore new treatment options should be considered.

Recently, immune checkpoint inhibitors have attracted attention and have shown to have both effectiveness and a very good toxicity profile. One of these classes of drugs is the anti-PD1 monoclonal antibodies and these are currently tested in different tumor types including NSCLC.

Stereotactic body radiation therapy (SBRT) is the delivery of a high dosis in generally 3-5 fractions with high accuracy taking into account tumor motion. SBRT has shown to be a successful treatment for tumors of the lung with sizes of < 5 cm and can be given in doses varying up to 3x18 Gy [23; 24]. Toxicity is very limited, but the treatment in lung cancer is until now restricted to early stages of lung cancer or oligometastatic disease [25]. Other organ sites suitable for SBRT are primary tumors and/or metastases of the e.g. brain, liver, adrenal gland and bone (spine) [26].

The traditional, palliative role of radiotherapy in metastatic disease is now evolving into that of a powerful initiator for immunotherapy [27; 28]. From different preclinical studies the expression of tumor antigens has shown to be up-regulated directly after radiotherapy and might therefore lead to changes in the immune response of the body. At this stage little is known about the impact of different total dose and fractionation regimens on the anti-tumor immune response [27]. Both SBRT and standard palliative treatment regimens such as 5x4 Gy have shown to be successful [29]. It is suggested that high doses of radiation (SBRT) to tumors may give rise to an abscopal effect as a result of the above mentioned mechanisms in certain patients. Therefore it is of great interest to investigate the effect of a treatment with SBRT, directly followed by the administration of pembrolizumab and to compare these results to treatment with pembrolizumab alone. Because little is known about the impact of different total dose and fractionation regimens on the anti-tumor immune response, a radiation regimen was chosen that results in: an adequate palliative dose, high accuracy with a limited number of fractions (SBRT) and low toxicity. Fraction size is similar to those used in immunogenic mice studies investigating anti-tumor response.

Since PD-L1 expression is not yet validated to be the best marker for immune modulation it is imperative that this study will be accompanied by a translational research focusing on factors involved in the immune response.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks

(Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the pembrolizumab program have shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). These early PK and pharmacodynamic data provide scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

4.2.3 Rationale for Endpoints

There is an urgent need to improve second and further lines of treatment in patients with NSCLC. The SOC has a very limited response rate (9%) and shows a marginal improvement in PFS and OS of respectively 4 and 9 weeks. This improvement is obtained at the costs of loss in QoL for those who do not respond. Currently, a phase III trial investigates the effect of pembrolizumab versus second line chemotherapy. Radiation therapy is currently only administered to metastatic disease for palliation We hypothesize that the tumor specific immune response will increase after SBRT to a single metastatic site due to the presentation of tumor related antigens and in doing so may enhance the effect of the pembrolizumab.

4.2.3.1 Efficacy Endpoints

This study will use the response rate, disease control rate, overall survival, progression free survival and toxicity as efficacy endpoints.

4.2.3.2 Biomarker Research

This study will use available, paired, tumor tissue and blood samples to:

- study the effect of immunotherapy on the size and diversity of lung carcinoma-specific T cell populations as measured by immune assays, including MHC tetramer technology and antigen-specific cytokine production.
- study the effect of immunotherapy on the cell numbers and activation status of CD4 and CD8 positive T cells, Tregs, MDSC and monocytes.
- examine effect of the immunotherapy on the immune infiltrates, PD-1 and PD-L1 expression within biopsies.
- examine the repertoire of potential T cell antigens in NSCLC lesions by genomic analysis.

These samples will also be used to identify possible biomarkers for selection of candidates for immunotherapy.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Proven diagnosis of recurrent Non-Small Cell Lung Cancer, both squamous or non-squamous carcinoma.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.

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

3. Have measurable disease based on RECIST 1.1.

4. Must provide newly obtained tissue from a core or excisional biopsy of a tumor lesion and are willing to have a second biopsy performed form any non-irradiated lesion after the radiation and immune-modulating treatment.

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Stage IV NSCLC; treated with at least 1 regimen of chemotherapy.

7. Have at least 2 separate (metastatic) lesions of which one is amenable for irradiation with a size of < 5 cm.

8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥50 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

9. Female subject of childbearing potential should have a negative urine or serum pregnancy test prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

11. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

4. Has had prior chemotherapy or targeted small molecule therapy within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

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

5. Have had previous radical radiation to any tumor site within 6 months prior to study Day 1.

6. Have known but untreated driver mutations of the EGFR gene or ALK translocation.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least six

weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to trial treatment.

9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjögren's syndrome will not be excluded from the study.

10. Has evidence of symptomatic interstitial lung disease or a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

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

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

19. Has had major surgery or major blood transfusions (>3 packed cells) in the past 3 months.

5.2 Trial Treatments

5.2.1 SBRT

In the experimental arm patients will be treated with pembrolizumab and randomized between no radiotherapy and SBRT. Multiple organ sites may be involved and it is up to the treating physician to decide what tumor localization to treat. Priority should be given to tumors, which likely will cause complaints in the near future. In any case normal tissue constraints (Table 2) should be met. Moreover, the minimal size of the tumor should be at least 0.5 cm with a maximum of 5 cm and radiotherapy treatment will be given 1-2 weeks prior to start of pembrolizumab.

5.2.1.1 Positioning of Patients.

Patients will be mostly positioned supine, but prone positioning is allowed. The use of an immobilization device (e.g. forearm support, T-bar, knee support, vacuum fixation box) is *obligated*, to ensure set-up reproducibility. Immobilization may be performed in accordance with each department's routine practice for subject positioning. All fields will be treated with the subject in the same position.

5.2.1.2 Respiration correlated planning CT

A 4D-CT scan in treatment position with 3 mm slice thickness will be made in case of lung, liver and adrenal gland tumors. In bone tumors or other metastatic sites, the treating physician will decide if a respiration correlated CT is necessary. A mid-position or mid-ventilation will be reconstructed from the 4D CT-scan, which is used for delineation and treatment planning. Other strategies to correct for tumor motion are allowed according to local policies. Reference lines should preferably be marked on the subject using tattoos.

5.2.1.3 Tumor delineation

The Gross Tumor Volume (GTV) will encompass the designated tumor using the appropriate window-level setting depending on the treated site, e.g. lung window level in case of a lung tumor. It is strongly recommended to use FDG-PET or MRI information if available.
The Clinical Tumor Volume (CTV) will encompass regions at risk for microscopic extension. Participating institutes are free to define their GTV to CTV margins. It is allowed to incorporate the CTV in the GTV to PTV margins, as done at the NKI.
The Planning Tumor Volume (PTV) will be generated by expansion of either the CTV or GTV using individualized margins in case of tumor motion. At the NKI baseline margins of lung tumors are 5-6 mm, liver and adrenal gland 9-10 mm and bone tumors 10 mm.

5.2.1.4 Organs at risk

The involved organs at risk located in close proximity of the designated tumor will be delineated. The organs at risk are mentioned in table 2.

5.2.1.5 Dose specification and treatment planning

The designated tumor will receive a treatment dose of 24 Gy, administered in fractions of 8 Gy on alternate days with a maximal overall treatment time of 10 days.
The treatment plan will be calculated using the available treatment planning system, which has a collapsed cone convolution superposition algorithm or an equivalent algorithm. The treatment plan will consist of multiple coplanar and/or non-coplanar 6-10 MV photon beams, taken into account normal tissue constraints (Table 2). Dose specification will be performed according to local policies and dose inhomogeneity in the PTV is allowed. At the NKI Volumetric Modulated Arc Therapy (VMAT) or static Intensity Modulated Radiotherapy (IMRT) will be used. Ninety-five per cent of the PTV should receive 100% of the prescribed dose. Dose inhomogeneity up to 165% of the prescribed dose is allowed in lung tumors, whereas in liver and adrenal gland tumors a maximum dose of 150% is allowed.

5.2.1.6 Treatment verification

Online image guidance is obliged. Before each treatment fraction, 3D or 4D images are acquired. An Cone Beam CT-scan or an in-room CT facility is used to acquire these images. At the NKI a bone match and soft tissue match is performed, in some cases with fiducials, followed by a couch shift, which is validated with a 2nd scan. During the dose delivery or at the end of the treatment fraction a third 3D or 4D-CBCT or room CT-scan is acquired to determine intra-fraction stability. Other online imaging protocols are allowed according to local policies.

Table 2: Organs at risk constraints

OAR's	Dose (Gy) SBRT 3 fractions
Bronchus	D0 ≤ 30 Gy
Brachial plexus	D0 ≤ 30 Gy
Colon	D0 ≤ 30 Gy
Duodenum	D0 ≤ 30 Gy
Esophagus	D0 ≤ 27 Gy
Great vessels	D0 ≤ 45 Gy (Lung)
	D0 ≤ 60 Gy (Liver)
Heart	D0 ≤ 30 Gy
Jejunum/ileum	D0 ≤ 27 Gy
Kidney	Vkidney – V15Gy ≥ 67%
Liver	Vliver – V15Gy ≥ 700 cc,
Lung	Dmean ≤ 16 Gy (NTD) V20 ≤ 10%
Spinal cord	D0 ≤ 18 Gy
Stomach	D0 ≤ 30 Gy D5cc ≤ 22.5 Gy

5.2.2 Dose Selection/Modification

5.2.2.1 Dose Selection Pembrolizumab

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

The treatment to be used in this trial is outlined below in table 3. The dose amount required to prepare the pembrolizumab infusion solution will be four vials containing 50 mg.

Table 3 Trial Treatment

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3w	IV infusion	3weeks	Experimental
The pembrolizumab is given as a flat dose					

Trial treatment should begin within 3 weeks after randomization for both arms.

5.2.2.2 Dose Modification Pembrolizumab

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 4 below.

Table 4: Dose modification guidelines for drug-related adverse events.

Toxicity	**Grade**	**Hold Treatment (Y/N)**	**Timing for restarting treatment**	**Dose/Schedule for restarting treatment**	**Discontinue Subject (after consultation with Sponsor)**
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3* *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and	Toxicity does not resolve within 12 weeks of last

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
• Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.6.1.1.		symptoms		schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	infusion
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

5.2.3 Timing of Dose Administration Pembrolizumab

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The MK-3475 Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2.4 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Patients will be randomized centrally into two arms.

Arm 1: High dose radiation (SBRT) followed by pembrolizumab treatment within 7 days after completion.

Arm 2: pembrolizumab treatment

The Trialoffice of the Biometrics Department at het NKI-AVL will randomise patients after completion of baseline investigations (phone +31 20 512 2668 or fax +31 20 512 2679). After checking eligibility criteria treatment will be assigned using the ALEA system and the patient will receive a unique sequence number. An automatic confirmation letter will be sent by e-mail to the participating investigator and to the datamanager involved.

5.4 Stratification

There is a stratification for never/hardly smokers vs ongoing/recent smokers planned in this study.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than pembrolizumab.
- Radical radiation therapy < 6 months prior start treatment
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or exacerbation of COPD. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

    - In subjects with severe enterocolitis (Grade 3), pembrolizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

    - In subjects with moderate enterocolitis (Grade 2), pembrolizumab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with pembrolizumab, see Section 5.2.

    - All subjects who experience diarrhea 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.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 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 infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** 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 po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (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 v4.0 (CTCAE) at http://ctep.cancer.gov		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

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

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 6.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
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	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis (> grade 1) should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 6.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (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 for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational 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 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 and to Merck. 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.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.6
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test

- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.

- Administrative reasons

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

5.9 Subject Replacement Strategy

A subject that discontinues from the trial may only be replaced in case of discontinuation before the response evaluation and/or second biopsy.

5.10 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**RT Phase**		**Treatment Cycles (+/- 3 days)**								**End of Treatment**	**Post-Treatment**		
								To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening (Visit 1)	RT (if applicable)	After RT treatment (when applicable) (Visit 2)˜	1˜	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits (patient without PD)	Survival Follow-Up (patient with PD or new treatment)
Scheduling Window (Days):	-28 to -1		+1 to +7		± 21	± 21	± 21	± 21	± 21	± 21	± 21	At time of discon	30 days post discon (or before new treatment)	Every 8 weeks post discon	Every 12 weeks
Administrative Procedures															
Informed Consent	x														
Inclusion/Exclusion Criteria	x														
Smoking status (active/recent vs never/hardly)	x														
Demographics and Medical History	x														
Prior and Concomitant Medication Review	x														
Trial Treatment Administration			x	x	x	x	x	x	x	x	x				
Post-study anticancer therapy status													x	x	x
Survival Status			x									x	x	x	x
Clinical Procedures/Assessment															
SBRT (3 x 8 Gy)		x													
Review Adverse Events	x		x		x	x	x	x	x	x	x	x	x		
Full Physical Examination	x														

Trial Period:	**Screening Phase**	**RT Phase**		**Treatment Cycles (+/- 3 days)**								**End of Treatment**	**Post-Treatment**		
								To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening (Visit 1)	RT (if applicable)	After RT treatment (when applicable) (Visit 2)˜	1˜	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits (patient without PD)	Survival Follow-Up (patient with PD or new treatment)
Scheduling Window (Days):	-28 to -1		+1 to +7		± 21	± 21	± 21	± 21	± 21	± 21	± 21	At time of discon	30 days post discon (or before new treatment)	Every 8 weeks post discon	Every 12 weeks
Directed Physical Examination			x		x	x	x	x	x	x	x	x		x	
Vital Signs and Weight	x		x		x	x	x	x	x	x	x	x	x	x	
ECOG Performance Status	x		x	x	x	x	x	x	x	x	x	x	x	x	
ECG (repeat when indicated)	x											x			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum β-HCG (WOCBP only)	x														
Hematology[1]	x		x^	x^	x	x	x	x	x	x	x	x	x		
Chemistry[2]	x		x^	x^	x	x	x	x	x	x	x	x	x		
ctDNA + Tumor markers[3]	x		x^	x^	x	x	x	x	x	x	x	x	x		
Coagulation[4]	x														
Endocrinology[5]	x				x	x			x+			x			
Urinalysis (when indicated)	x														
Efficacy Measurements															
Tumor Imaging (CT scan and/or ultra-sound)	x				x		x		x		x	x		x	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood															

Trial Period:	**Screening Phase**	**RT Phase**		**Treatment Cycles (+/- 3 days)**								**End of Treatment**	**Post-Treatment**		
								To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening (Visit 1)	RT (if applicable)	After RT treatment (when applicable) (Visit 2)~	1~	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits (patient without PD)	Survival Follow-Up (patient with PD or new treatment)
Scheduling Window (Days):	-28 to -1		+1 to +7		± 21	± 21	± 21	± 21	± 21	± 21	± 21	At time of discon	30 days post discon (or before new treatment)	Every 8 weeks post discon	Every 12 weeks
Newly Obtained Tissue Collection	x				x#										
Correlative Studies Blood Collection[6]	x		x*^	x^	x	x	x	x	x	x	x	x	x		

~: Same visit, only RT arm requires more investigations.

*: Preferably one week after the end of the SBRT

#: Previously irradiated lesions are not considered suitable for biopsy and response evaluation. The biopsy is performed before cycle 3.

^: Blood collection in both arms will be performed on the same day as the first dose of the study medication.

+: C3, C6, C10, C14, C18, every 4th cycle, EOT

1: Hb, Ht, RBC (incl. MCV, MCH, MCHC), WBC, Plt, NeutroGran, Diff-white

2: BiliTot, AF, AST, ALT, LDH, creat, BUN, Sodium, Potassium, Mg, Calcium, Gluc Total protein, Albumin,

3: CEA, CA125, NSE, SCC, Cyfra 21.1

4: PT (INR), APTT

5: TSH, T4

6: At Screening, Cycle 2, Cycle 3 and End of Treatment: 50 ml blood will be collected. At all other visits 20 ml blood will be collected for correlative studies.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

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

the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.7 Assignment of Screening Number

Patients will receive a pre-registration number at the Trial Office.

7.1.1.8 Assignment of Randomization Number

All patients will receive a randomization number at the Trial Office.

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

Compliance will be recorded in the medical records.

7.1.2 Clinical Procedures/Assessments

The clinical procedures will be recorded in the medical records.

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE).

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

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

At all other visits the investigator or qualified designee will perform a directed physical exam (see Trial Flow Chart) as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG Performance status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor evaluation will take place every 6 weeks by RECIST 1.1. In case of new lesions or moderate growth of the lesions in the pembrolizumab arm, the physician can decide to continue treatment for another 6 weeks if considered to be in the best interest of the patient.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

According to the protocol, blood samples will be collected according to the Trial Flow Chart in all arms . Tissue samples will be collected before start of the treatment and after 3-6 weeks of treatment with pembrolizumab. The tumor biopsies will be anonymized and stored for a maximum of 15 years.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in the Trial Flow Chart.
Laboratory tests for screening or entry into the study should be performed within -28 to -1 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

There are no PK/PD studies planned.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2..

7.1.4.2 Blinding/Unblinding

Not applicable

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period

The screening will be performed timely before start of the study. Scans and ultrasound examinations should be performed within 28 days before start of treatment.

In case of radiation therapy the CT scan or ultra-sound must be repeated when the time exceeds the 28 days.

7.1.5.1.2 Treatment Period

The study will start in January 2015 with first patient in February. It is planned to have the last patient included in May 2016.

7.1.5.2 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.3 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression should be assessed every 8 weeks by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins any new treatment.

7.1.5.3.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the NKI Datacenter and the NKI Datacenter will report it within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the NKI Datacenter and the NKI Datacenter will report it within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 10 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the NKI Data Center and the NKI Data Center will report it within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

The SAE reports must be made by fax (020-512 26 79) to the NKI Data Center between 09.00 and 17.00 hours Monday to Friday.

The NKI Data Center will forwarded all SAE reports and any other relevant safety information to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

Reporting must be done using the Serious Adverse Event Form of the study. The forms will be filed at the NKI Data Center.
All serious adverse events must be followed up until resolution or stabilization, and this information must be reported to the Data Center as soon as it becomes available, using a follow-up Serious Adverse Event Form. This form will be signed by the investigator and filed together with the initial report. All SAE's will be reported once yearly, as described in the section " Annual safety report". SAE's for this multicenter oncological study will not be reported through the web portal ToetsingOnline to the METC.

7.2.3.2 **Reporting of SUSARs**

The NKI is the sponsor of this study. The Data Center will represent the NKI for the sponsor task of reporting safety data according to the WMO requirements. The NKI Data Center personnel will notify the study coordinator of any serious adverse event reported. The study coordinator will evaluate the SAE and will decide whether the event reported could be related to the protocol treatment and whether it is, both, unexpected and serious (SUSAR). The Data Center will report all SUSARs through the web portal ToetsingOnline to the METC. This reporting will be expedited and will occur not later than 15 days after the Data Center has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

7.2.3.3 **Annual safety report**

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.
This safety report consists of:

– a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;

– a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

7.2.3.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the NKI Data Center and the NKI Data Center will report within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Events of clinical interest for this trial include:

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

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

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

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event:

   a. Grade ≥ 3 diarrhea

b. Grade ≥ 3 colitis
c. Grade ≥ 2 pneumonitis
d. Grade ≥ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event.

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

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the NKI Data Center and the NKI Data Center will report it to Merck Global Safety within 2 working days.

7.2.4 Evaluating Adverse Events

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

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

Table 10 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

8.2 Statistical Analysis Plan

The primary endpoint of the study is Overall Response Rate at 12 weeks. Patients having a partial response or complete response at 12 weeks are considered successes, while all other situations are considered failures.

The hypothesis of the trial is that pembrolizumab administered after SBRT will increase the Overall Response Rate from 20% by pembrolizumab alone to 50% by pembrolizumab after SBRT.

Assumptions:

It is expected that in the pembrolizumab alone arm an Overall Response rate of 20% will be observed at 12 weeks [33]. The hypothesis is that pembrolizumab after SBRT may at least increase double the Overall Response Rate to 50% at 12 weeks. Patients will be randomized in a 1:1 ratio (pembrolizumab +/- SBRT).

A Fisher's exact test with a 0.10 two-sided significance level will have 82% power to detect the difference between standard response rate of 20% and a SBRT + pembrolizumab response rate of 50% (odds ratio of 4) when the sample size is 37 patients per arm, or 74 patients in total.

Secondary endpoints will be

- DCR, defined as the percentage of patients having a complete response, partial response or stable disease at 12 weeks,
- PFS, defined as time from randomization to disease progression or death,
- OS, defined as time from randomization to death (of any cause).
- Toxicity

Randomization will be performed according to a minimization algorithm, stratified by smoking status (non-smokers vs rest).

The primary analysis will be performed on the intention-to-treat population. The response rate at 12 weeks will be compared by means of a Fisher’s exact test of pembrolizumab after SBRT with pembrolizumab alone.

Exploratory analysis will be performed on the comparison between biopsies before and after treatment administration and between both pembrolizumab arms.

Toxicity will be analyzed in patients who have received at least one administration of pembrolizumab.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab 50 mg	Lyo formulation

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

All data will be part of the medical record and be kept confidential.

10.2 Compliance with Financial Disclosure Requirements

These will be executed according to local rules and regulations.

10.3 Compliance with Law, Audit and Debarment

These will be executed according to local rules and regulations.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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.

10.5 Quality Management System

These will be executed according to local rules and regulations.

10.6 Data Management

The Datacenter of the NKI will be responsible for all registration purposes and collection of the data. All data that are relevant for the study will be collected in an eCRF. All SAE's, whether or not deemed drug related or expected, must be recorded in an eCRF AE- form. It is critical that the information provided on the SAE-form matches the information recorded in the eCRF for the same event.

The completed eCRFs must be reviewed, signed and dated by the Principal Investigator or sub-investigator.
Data cleaning procedures will be performed as described in de Data Validation Plan. An overall description of all data management procedures will be documented in a study-specific Data Management Plan. In addition the statistical analysis will be carried out.

10.7 Study Monitoring

Monitoring according to ICH GCP will be performed by the Clinical Research Monitor of the NKI-AVL or the person to whom the monitoring tasks have been delegated. Amongst others the following will be reviewed:

- Compliance with the protocol, ICH_GCP and all applicable regulatory requirements.
- Consent procedures, including date of consent and signatures
- Study progress

(Serious) Adverse Events

Completion of the (e)CRFs and verification of data against the source data. Storage, dispensing and accountability of study medication.

Details of the extent of monitoring will be described in the study specific Monitoring Plan.

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11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

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

11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

* As published in the European Journal of Cancer:

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

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