

**Randomized phase II study of immune stimulation with  
Pembrolizumab and radiotherapy in second line therapy  
of metastatic head and neck squamous cell carcinoma  
(IMPORTANCE)**

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**Product:** Pembrolizumab



2

**Protocol/Amendment No.: 717**

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**TABLE OF CONTENTS**

<b>1.0</b>	<b>TRIAL SUMMARY.....</b>	<b>10</b>
<b>2.0</b>	<b>TRIAL DESIGN.....</b>	<b>12</b>
2.1	Trial Design .....	12
2.2	Trial Diagram.....	13
<b>3.0</b>	<b>OBJECTIVES &amp; HYPOTHESES.....</b>	<b>13</b>
3.1	Primary Objective & Hypothesis .....	13
3.2	Secondary Objectives & Hypotheses.....	14
3.3	Exploratory Objective .....	14
<b>4.0</b>	<b>BACKGROUND &amp; RATIONALE.....</b>	<b>14</b>
4.1	Background .....	14
4.1.1	Pharmaceutical and Therapeutic Background.....	14
4.1.2	Preclinical and Clinical Trial Data.....	16
4.1.2.1	Current treatment of metastatic head and neck squamous cell carcinoma ..	16
4.1.2.2	Pembrolizumab in different tumor entities .....	16
4.1.2.3	Pembrolizumab in head and neck squamous cell carcinoma (HNSCC).....	17
4.1.2.4	The medical challenge .....	18
<b>4.2</b>	<b>Rationale .....</b>	<b>18</b>
4.2.1	Rationale for the Trial .....	18
4.2.1.1	Abscopal effects of radiotherapy combined with immune therapy .....	18
4.2.1.2	Upregulation of Programmed cell death ligand 1 (PD-L1) by radiotherapy .....	19
4.2.1.3	Radiotherapy and PD-1/ PD-L1 pathway blockade in vitro .....	19

**Protocol/Amendment No.: 717**

4.2.1.4	Fractionation of radiotherapy.....	19
4.2.1.5	Timing of radiotherapy and pembrolizumab administration .....	20
4.2.2	Rationale for pembrolizumab Dose Selection/ Regimen/ Modification.....	20
4.2.3	Rationale for Endpoints .....	21
4.2.3.1	Efficacy Endpoints.....	21
4.2.3.2	Safety endpoints.....	21
4.2.3.3	Biomarker Research.....	21
4.2.4	Risk-benefit analysis .....	21
<b>5.0</b>	<b>METHODOLOGY .....</b>	<b>23</b>
<b>5.1</b>	<b>Entry Criteria.....</b>	<b>23</b>
5.1.1	Diagnosis/ Condition for Entry into the Trial .....	23
5.1.2	Subject Inclusion Criteria.....	23
5.1.3	Subject Exclusion Criteria .....	25
<b>5.2</b>	<b>Trial Treatments .....</b>	<b>28</b>
5.2.1	Treatment with pembrolizumab .....	28
5.2.1.1	Dose Selection .....	28
5.2.1.2	Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy .....	29
5.2.2	Treatment with Radiotherapy.....	35
5.2.2.1	Technical factors of Radiotherapy.....	35
5.2.2.2	Immobilization and planning CT scan .....	35
5.2.2.3	Target volumes.....	35
5.2.2.4	Dose prescription and dose specification of Radiotherapy.....	36
5.2.2.5	Dose modification of Radiotherapy .....	36

## Protocol/Amendment No.: 717

5.2.2.6	Documentation requirements and portal films.....	36
5.2.2.7	Critical normal structures and adverse events of radiotherapy .....	36
5.2.3	Adverse events of radiotherapy combined with pembrolizumab.....	38
5.2.4	Timing of Administration of pembrolizumab and Radiotherapy.....	39
5.2.5	Trial Blinding/ Masking.....	39
<b>5.3</b>	<b>Randomization or Treatment Allocation.....</b>	<b>39</b>
<b>5.4</b>	<b>Stratification.....</b>	<b>39</b>
<b>5.5</b>	<b>Concomitant Medications/ Vaccinations (allowed &amp; prohibited) .....</b>	<b>40</b>
5.5.1	Acceptable Concomitant Medications .....	40
5.5.2	Prohibited Concomitant Medications/ Therapies.....	40
<b>5.6</b>	<b>Rescue Medications &amp; Supportive Care .....</b>	<b>41</b>
5.6.1	Supportive Care Guidelines pembrolizumab .....	41
5.6.2	Additional supportive Care Guidelines Radiotherapy .....	45
<b>5.7</b>	<b>Diet/ Activity/ Other Considerations.....</b>	<b>45</b>
5.7.1	Diet.....	45
5.7.2	Contraception .....	45
5.7.3	Use in Pregnancy .....	47
5.7.4	Use in Nursing Women.....	47
<b>5.8</b>	<b>Subject Withdrawal/ Discontinuation Criteria .....</b>	<b>48</b>
5.8.1	Discontinuation of Study Treatment after CR .....	49
<b>5.9</b>	<b>Subject Replacement Strategy .....</b>	<b>49</b>
<b>5.10</b>	<b>End of the trial .....</b>	<b>49</b>
<b>5.11</b>	<b>Clinical Criteria for Early Trial Termination .....</b>	<b>49</b>

## Protocol/Amendment No.: 717

<b>6.0</b>	<b>TRIAL FLOW CHART .....</b>	<b>50</b>
<b>6.1</b>	<b>Study Flow Chart.....</b>	<b>50</b>
<b>7.0</b>	<b>TRIAL PROCEDURES .....</b>	<b>55</b>
<b>7.1</b>	<b>Trial Procedures .....</b>	<b>55</b>
7.1.1	Administrative Procedures.....	55
7.1.1.1	Informed Consent.....	55
7.1.1.1.1	General Informed Consent.....	55
7.1.1.2	Inclusion/ Exclusion Criteria .....	56
7.1.1.3	Demographics and Medical History .....	56
7.1.1.4	Prior and Concomitant Medications Review .....	56
7.1.1.4.1	Prior Medications.....	56
7.1.1.4.2	Concomitant Medications .....	56
7.1.1.5	Disease Details and Treatments .....	56
7.1.1.5.1	Disease Details.....	56
7.1.1.5.2	Prior Treatment Details.....	56
7.1.1.5.3	Subsequent Anti-Cancer Therapy Status .....	57
7.1.1.6	Assignment of Screening Number .....	57
7.1.1.7	Assignment of Randomization Number.....	57
7.1.2	Clinical Procedures/ Assessments.....	58
7.1.2.1	Adverse Event (AE) Monitoring.....	58
7.1.2.2	Full Physical Examination .....	58
7.1.2.3	Directed Physical Examination.....	58
7.1.2.4	Vital Signs.....	58

**Protocol/Amendment No.: 717**

7.1.2.5	Electrocardiogram.....	58
7.1.2.6	Eastern Cooperative Oncology Group (ECOG) Performance Scale .....	59
7.1.2.7	Tumor Imaging and Assessment of Disease .....	59
7.1.2.8	Tumor Tissue Collection and Correlative Studies Blood Sampling.....	59
7.1.3	Laboratory Procedures/ Assessments.....	59
7.1.4	Other Procedures .....	61
7.1.4.1	Withdrawal/ Discontinuation from study.....	61
7.1.4.2	Blinding/ Unblinding .....	61
7.1.4.3	Patient questionnaires .....	61
7.1.5	Visit Requirements.....	61
7.1.5.1	Screening.....	61
7.1.5.2	Treatment Period.....	62
7.1.5.3	End of Treatment Visit.....	62
7.1.5.4	Post-Treatment Visits.....	63
7.1.5.4.1	Safety Follow-Up Visit.....	63
7.1.5.4.2	Follow-up Visits .....	63
7.1.5.4.3	Survival Follow-up .....	63
7.1.5.5	Aftertreatment .....	63
<b>7.2</b>	<b>Assessing and Recording Adverse Events .....</b>	<b>64</b>
7.2.1	Definition of an Overdose for this Protocol and Reporting of Overdose .....	65
7.2.2	Reporting of Pregnancy and Lactation.....	66
7.2.3	Immediate Reporting of Adverse Events .....	66
7.2.3.1	Serious Adverse Events .....	66

## Protocol/Amendment No.: 717

7.2.3.2	Events of Clinical Interest.....	68
7.2.3.3	Protocol-Specific Exceptions to Serious Adverse Event Reporting .....	69
7.2.4	Evaluating Adverse Events .....	69
7.2.5	Sponsor Responsibility for Evaluating and Reporting Adverse Events .....	75
7.2.6	Data Safety Monitoring Committee (DSMC).....	75
<b>8.0</b>	<b>STATISTICAL ASPECTS.....</b>	<b>75</b>
<b>8.1</b>	<b>Trial design and primary hypotheses.....</b>	<b>75</b>
<b>8.2</b>	<b>Sample size calculation .....</b>	<b>76</b>
<b>8.3</b>	<b>Evaluation categories of patients.....</b>	<b>76</b>
<b>8.4</b>	<b>Methods of statistical analysis .....</b>	<b>77</b>
<b>8.5</b>	<b>Statistical Analysis Plan .....</b>	<b>78</b>
<b>9.0</b>	<b>LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES .....</b>	<b>78</b>
<b>9.1</b>	<b>Investigational Product .....</b>	<b>78</b>
<b>9.2</b>	<b>Packaging and Labeling Information .....</b>	<b>78</b>
<b>9.3</b>	<b>Clinical Supplies Disclosure.....</b>	<b>78</b>
<b>9.4</b>	<b>Storage and Handling Requirements.....</b>	<b>78</b>
<b>9.5</b>	<b>Returns and Reconciliation.....</b>	<b>79</b>
<b>10.0</b>	<b>ADMINISTRATIVE AND REGULATORY DETAILS.....</b>	<b>79</b>
<b>10.1</b>	<b>Confidentiality.....</b>	<b>79</b>
<b>10.2</b>	<b>Compliance with Financial Disclosure Requirements.....</b>	<b>79</b>
<b>10.3</b>	<b>Compliance with Law, Audit and Debarment .....</b>	<b>80</b>
<b>10.4</b>	<b>Compliance with Trial Registration and Results Posting Requirements .....</b>	<b>80</b>
<b>10.5</b>	<b>Quality Management System.....</b>	<b>80</b>

Protocol/Amendment No.: 717

10.6	Data Management and Data Archiving .....	80
11.0	TRANSLATIONAL RESEARCH .....	82
11.1	Immune status in the peripheral blood .....	82
11.2	PD-L1 in combination with tumor-infiltrating lymphocytes .....	83
12.0	REFERENCES .....	84
13.0	Abbreviations .....	88
14.0	APPENDICES .....	92
14.1	ECOG Performance Status .....	92
14.2	Common Terminology Criteria for Adverse Events V4.0 (CTCAE) .....	92
14.3	Response Evaluation Criteria iRECIST .....	92
15.0	Signatures .....	94
15.1	Sponsor's Representative .....	94
15.2	Investigator .....	95

## Protocol/Amendment No.: 717

## 1.0 TRIAL SUMMARY

Title	Randomized phase II study of <u>i</u> mmune stimulation with <u>P</u> embrolizumab and <u>r</u> adiotherapy in second line therapy of metastatic head and <u>n</u> eck squamous <u>c</u> ell carcinoma
Abbreviated Title:	Pembrolizumab and Radiotherapy in metastatic HNSCC
EudraCT NUMBER:	2017-002122-20
Protocol code:	IMPORTANCE (Keynote-717)
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Trial Phase	<i>Phase II</i>

## Protocol/Amendment No.: 717

Clinical Indication	<p>Metastatic HNSCC</p> <p><u>OR</u></p> <p>Locally recurrent HNSCC not suitable for local treatment (at least two lesions, e.g. primary tumor and lymph node)</p> <p>Progression to first line platinum-based or any second/ third line chemotherapy</p> <p><u>OR</u></p> <p>Progression within 6 months after platinum-based radiochemotherapy of locally advanced disease</p> <p><u>OR</u></p> <p>First line treatment if PD-L1 CPS (combined positive score) <math>\geq 1</math></p>
Trial Type	Multicenter prospective clinical trial
Type of control	Randomized trial
Route of administration	Pembrolizumab i.v. and percutaneous radiotherapy
Trial Blinding	none (open-label)
Treatment Groups	<p>A: Pembrolizumab (200mg absolute, q3w) combined with radiotherapy (12x3Gy) of one, two or three tumor lesions. Only lesions that perspective require radiotherapy will be treated. The irradiated tumor volume must be at least 2ml. Radiotherapy of brain metastases is not allowed.</p> <p>B: Pembrolizumab (200mg absolute, q3w)</p>
Primary endpoint	Response to treatment according to iRECIST (irradiated lesion are excluded).
Number of trial subjects	130
Estim. enrollment period	<i>24 months</i>
Estimated duration of trial	<i>36 months</i>
Duration of Participation	12 months (treatment)
Estimated average length of treatment per patient	6 months

## **2.0 TRIAL DESIGN**

### **2.1 Trial Design**

This is an open-label, randomized, prospective, multicenter phase II clinical trial of pembrolizumab with or without local radiotherapy in patients with recurrent and/ or metastatic HNSCC after progression to platinum-based therapy or as first line treatment if CPS $\geq$ 1.

All patients will receive pembrolizumab 200mg absolute dose administered every third week. Patients in treatment arm A will receive radiotherapy of one, two or three tumor lesions with a total tumor volume of at least 2ml intended to induce tumor cell death acting as an in situ vaccination. If possible, the irradiated tumor volume should be  $\geq$ 5ml. Radiotherapy will be performed conventionally fractionated with single doses of 3Gy to a total dose of 36Gy. There will be a strict time schedule. Radiotherapy will always start on Wednesday. After application of the third radiation dose (Friday) the patients will receive pembrolizumab. After an interruption of radiotherapy for two days (Saturday, Sunday), radiotherapy will be continued. Pembrolizumab will be continued on an every three week schedule until confirmed disease progression according to iRECIST criteria, unacceptable toxicity, patient's wish to stop therapy or a maximal treatment time of 12 months.

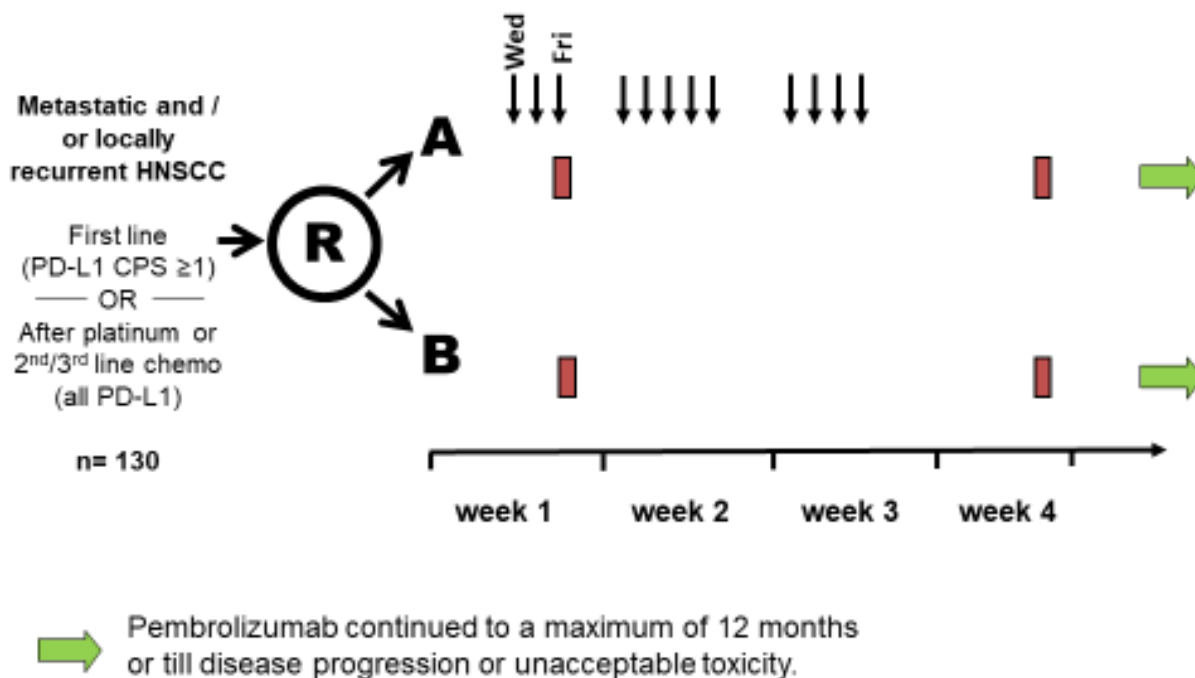
Tumor assessment will be performed every 9 weeks and will be evaluated according to iRECIST and RECIST (see Appendix 14.3). For each patient the same assessment method will be used throughout the study. Toxicity will be assessed according to revised NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE 4.0) (see Appendix 14.2).

Protocol/Amendment No.: 717

## 2.2 Trial Diagram

↓ RT: 12 x 3.0 Gy (36.0 Gy) administered to one, two or three tumor lesions

■ Pembrolizumab: 200mg absolute dose (q3w)



## 3.0 OBJECTIVES & HYPOTHESES

### 3.1 Primary Objective & Hypothesis

(1) **Objective:** Assessment of the effect of local radiotherapy on systemic response to pembrolizumab

**Hypothesis:** Local radiotherapy will significantly improve the overall response rate according to iRECIST

### 3.2 Secondary Objectives & Hypotheses

- (1) **Objective:** Assessment of the effect of local radiotherapy on different response criteria to pembrolizumab

**Hypothesis:** Local radiotherapy will tend to improve:

- Response rate according to RECIST
- changes of (not irradiated) target lesion
- duration of response
- progression free survival
- overall survival

- (2) **Objective:** Assessment of safety and tolerability of the combination of pembrolizumab and radiotherapy

**Hypothesis:** Local radiotherapy will not increase toxicity grade 3 or higher according to CTCAE 4.0

### 3.3 Exploratory Objective

- (1) **Objective:** Assessment of changes of the immunophenotype in peripheral blood after pembrolizumab without and with radiotherapy (longitudinal analysis)
- (2) **Objective:** Assessment of predictive value of PD-L1 in combination with tumor-infiltrating lymphocytes

## 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. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8<sup>+</sup> T-cells and the ratio of CD8<sup>+</sup> effector T-cells/ FoxP3<sup>+</sup> regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

**Protocol/Amendment No.: 717**

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/ or PD-L2). The structure of murine PD-1 has been resolved. 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 CD3 $\zeta$ , PKC $\theta$  and ZAP70 which are involved in the CD3 T-cell signaling cascade. 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. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8<sup>-</sup> (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with cancer. 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 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. Keytruda<sup>TM</sup> (pembrolizumab) has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor and PD-L1 expressing non-small cell lung cancer (NSCLC) after first line chemotherapy. Recently, pembrolizumab 200mg fixed dose administered every three weeks was approved in HNSCC by the FDA.

## **4.1.2 Preclinical and Clinical Trial Data**

### **4.1.2.1 Current treatment of metastatic head and neck squamous cell carcinoma**

Head and neck squamous cell cancer (HNSCC) is the 7<sup>th</sup> most common cancer worldwide. The current standard of care for palliative chemotherapy of metastatic HNSCC is a platinum combination mostly combined with cetuximab. The addition of cetuximab to cisplatin and 5-fluorouracil was the most recent treatment change in metastatic HNSCC (EXTREME trial)<sup>1</sup>. But despite a high overall response rate of 36% and disease control rate of 81% median overall survival with this scheme is only 10 months. A further intensification with the addition of docetaxel did not improve treatment results (CEFCID trial)<sup>2</sup>. In a phase II trial the combination of cisplatin, docetaxel and cetuximab was safer and also seems to be effective<sup>3</sup>. This scheme is currently studied in the ongoing phase III TPExtreme trial (NCT02268695). In second line treatment methotrexate or taxanes are frequently used. Second line treatment with methotrexate alone or in combination with 5FU shows a median overall survival of only approximately 7 months<sup>4,5</sup>. The median overall survival of second line docetaxel is also only 6 months<sup>6</sup>. New agents as the tyrosine kinase inhibitor gefitinib or the PI3-kinase inhibitor PX-866 failed to improve treatment results<sup>4-6</sup>.

### **4.1.2.2 Pembrolizumab in different tumor entities**

The strategy of releasing a suppressed immune reaction was successful in several tumor entities. As mentioned above pembrolizumab has been approved by the FDA and EMA for metastatic melanoma and PD-L1 NSCLC. The most important clinical trials are shown in table 1.

## Protocol/Amendment No.: 717

Table 1: Most important clinical trials with pembrolizumab.

Trial	Entity	Treatment	Patients	ORR	Survival	Response duration
KEYNOTE-001 (Garon et al <sup>7</sup> )	NSCLC	Pem (2 or 10 mg/kg in q2w or q3w)	495	19.4%	Median OS: 12.0 mo.	Median: 12.5 mo.
KEYNOTE-002 (Ribas et al <sup>8</sup> )	Melanoma after Ipi. / BRAFi	Pem 2mg/kg vs. Pem 10mg/kg vs. investigators choice chemotherapy	180 / 181 / 179	21% / 25% / 4%	6-mo. PFS: 34% / 38% / 16 %	Median: not reached
KEYNOTE-006 (Robert et al <sup>9</sup> )	Melanoma	Pem 10mg/kg q2w vs. q3w vs. Ipi.	279 / 277 / 278	33.7% / 32.9% / 11.9%	OS 1year: 74.1% / 68.4% / 58.2%	Ongoing (FU 8mo) 89%/97% / 88%
KEYNOTE-10 (Herbst et al <sup>10</sup> )	PD-L1+ NSCLC after platinum	Pem 2mg/kg vs. Pem 10mg/kg vs. Docetaxel	344 / 346 / 343	18% / 18% / 9%	Median OS: 10.4 mo. / 12.7 mo. / 8.3 mo.	Median: n.r. / n.r. / 8 mo.
NCT02267603 (Nghiem et al <sup>11</sup> )	Merkel cell carcinoma	Pem 2mg/kg q3w	26	56%	PFS 6 mo.: 67%	Range >2-7 mo.
KEYNOTE-12 (Muro et al <sup>12</sup> )	PD-L1+ Gastric Cancer	Pem 2mg/kg q2w	39	22%	-	Median: 9.2 mo.
KEYNOTE-12 (Seiwert et al <sup>13</sup> )	HNSCC	Pem 200mg fix dose q3w	132	24,8%	-	Range >2-6 mo.

In the large clinical trials in NSCLC and melanoma despite low objective response rates between 18% and 33%, overall survival improved significantly<sup>7-9</sup>. This is based on the finding that if a response appears, it is a long-lasting response. This observation has also been made with other immune therapies.

#### 4.1.2.3 Pembrolizumab in head and neck squamous cell carcinoma (HNSCC)

Recently, in the KEYNOTE-12 clinical trial pembrolizumab was also effective in second line therapy of metastatic HNSCC. In this trial with 132 patients, the overall response rate to pembrolizumab was 24.8% and further 24.8% had stable disease. In interpreting these results,

**Protocol/Amendment No.: 717**

it has to be considered, that 59.1% of the patients had at least two prior therapies. Interestingly, the responses to pembrolizumab were durable, with 86% of the patients still responding at the time point of the interim analysis (median follow-up duration 5.7 months)<sup>13</sup>. The similar PD-1 inhibitor nivolumab was tested in the CHECKMATE-141 trial as second line therapy against investigator's choice of chemotherapy. After 361 randomized patients this study was stopped because the PD-1 inhibitor significantly improved OS after 12 months from 16.6% to 36.0%. Interestingly, this overall survival benefit is based on a low overall response rate of only 13.3% and a stable disease in 22.9% of the patients<sup>14</sup>. Similar trials with pembrolizumab in second line (KEYNOTE-040/NCT02252042 or KEYNOTE-55/NCT02255097) and even first line therapy are currently ongoing (KEYNOTE-48/NCT02358031). Recently, Pembrolizumab has been approved in HNSCC by the FDA.

**4.1.2.4 The medical challenge**

It is generally assumed, that an improvement of the response rate will directly result in a further improvement of OS. Based on this assumption, pembrolizumab is combined with different agents in several clinical trials with the aim to improve the response rate. Most recent strategies are combinations of pembrolizumab with a histone deacetylase inhibitor, a bruton kinase inhibitor or even oncolytic viruses (NCT02538510, NCT02454179, NCT02626000). In a clinical trial with the other PD-1 inhibitor nivolumab in metastatic melanoma the combination with the CTLA-4 antibody ipilimumab increased the response rate to 57.6%. But with this treatment 68.7% of the patients suffered treatment related toxicities grade 3 or 4<sup>15</sup>. Especially in the palliative setting, such severe toxicities should be avoided in respect of quality of life. Thus the current medical challenge is to find a combination treatment partner for PD-1 inhibitors to improve the response rate without a severe increase of toxicity.

**4.2 Rationale****4.2.1 Rationale for the Trial****4.2.1.1 Abscopal effects of radiotherapy combined with immune therapy**

Combination of radiotherapy with pembrolizumab is currently studied in locally advanced HNSCC (NCT02609503, NCT02586207) and in re-irradiations (NCT02289209) with the aim to improve local tumor control. But radiotherapy not only kills tumor cells, but also changes the tumor cell phenotype and the tumor microenvironment, which might result in induction of anti-tumor immune responses<sup>16</sup>. The latter act locally on the irradiated tumor and systemically on non-irradiated tumor masses, the so called "abscopal effect" of radiotherapy<sup>17</sup>. These systemic effects of local radiotherapy mostly occur in combination with further immune modulation<sup>18</sup> and have already been reported in patients in combination with anti-CTLA-4 therapy in different tumor entities<sup>19-21</sup>. In a retrospective analysis of 21 melanoma patients with progression under anti-CTLA-4, radiotherapy re-induced a systemic treatment response in

## Protocol/Amendment No.: 717

more than half of the patients<sup>22</sup>. This was not dependent of the location of the irradiated metastasis. In another retrospective clinical analysis of patients treated with CTLA-4 blockade shrinkage of not irradiated index lesions occurred more frequently if radiotherapy and immunotherapy was administered within 3 months compared to longer time intervals<sup>23</sup>. Furthermore, in a prospective clinical trial with radiotherapy and granulocyte-macrophage colony-stimulating factor, systemic effects of local radiotherapy (10x3,5Gy) were achieved in 11 of 41 patients with different solid tumors<sup>24</sup>.

#### 4.2.1.2 Upregulation of Programmed cell death ligand 1 (PD-L1) by radiotherapy

PD-L1 is the ligand of PD-1 and can be found on cancer cells and immune cells. In a meta-analysis of different tumor entities high cancer cell PD-L1 expression was associated with an improved response rate to pembrolizumab<sup>25</sup>. In the CHECKMATE-141 trial in HNSCC the PD-1 inhibitor nivolumab especially improved overall survival in the PD-L1 positive subgroup<sup>14</sup>. *In vitro* radiotherapy induces an up-regulation of PD-L1<sup>26</sup> (and own unpublished data). This up-regulation has recently been confirmed in cancer patients, when PD-L1 status was compared before and after radiotherapy<sup>27,28</sup>. In preclinical experiments fractionated radiotherapy induced a stronger up-regulation of PD-L1 than a single high dose (own unpublished data). The maximal increase of PD-L1 was detected three days after fractionated radiation *in vitro*<sup>26</sup>.

#### 4.2.1.3 Radiotherapy and PD-1/ PD-L1 pathway blockade in vitro

In preclinical experiments the combination of radiotherapy and PD-1/ PD-L1 pathway blockade improved local tumor control<sup>26,29,30</sup>. But this combination also induced systemic tumor immunity. Consequently, metastases distant from the irradiated tumor responded after radiotherapy and the survival rate of the animals improved<sup>26,29</sup>. Thus, local radiotherapy, acting as *in situ* vaccination, is probably able to improve the response rate to pembrolizumab in recurrent and/ or metastatic HNSCC.

#### 4.2.1.4 Fractionation of radiotherapy

As mentioned above, PD-L1 expression increases especially after fractionated radiation. In preclinical models the combination of CTLA-4 blockade induced more abscopal effects with fractionated radiotherapy compared to the application of one single high radiation dose<sup>31</sup>. Clinical analyses of patients treated with radiotherapy and CTLA-4 blockade revealed that radiation doses up to 3Gy more frequently induce abscopal effects than higher doses<sup>32</sup>. In a prospective clinical trial with radiotherapy and granulocyte-macrophage colony-stimulating factor, systemic effects of fractionated radiotherapy with 10x3,5Gy were induced in 11 of 41 patients<sup>24</sup>. Thus in this trial a radiotherapy with 12 fractions of 3Gy (cumulative dose 36Gy) was chosen. This is a clinical standard dose for palliative radiotherapy of bone, lymphatic node or soft tissue metastases. This dose can also easily be delivered to organ metastases in lung, liver or the adrenal glands with a stereotactic technique and organ motion management.

## Protocol/Amendment No.: 717

**4.2.1.5 Timing of radiotherapy and pembrolizumab administration**

To achieve a maximal immune stimulation after radiotherapy the timing of the administration of pembrolizumab must be critically reviewed. In a clinical analysis overall survival was best if a radiotherapy and immune therapy with CTLA-4 blockade was administered concomitantly<sup>33</sup>. Regarding the timing of PD-1 inhibitors only preclinical analyses exist. PD-L1 expression peaked three days after fractionated radiation (5x2 Gy)<sup>26</sup>. In a preclinical setting survival of tumor bearing mice was better when PD-1/ PD-L1 blockade was administered during radiotherapy compared to after radiotherapy. Application with the first radiation showed a slight advantage compared to application with the last radiation<sup>26</sup>. Taken together, current preclinical and first clinical data indicate the best immune stimulating effect for early concomitant administration of the immune stimulating agent. Consequently, in this trial pembrolizumab is administered after the third fraction of radiotherapy consisting of altogether 12 fractions. As radiotherapy always starts on Wednesday, after the administration of pembrolizumab will always be two days without radiotherapy (Saturday and Sunday). This ensures that radiotherapy does not impede the initiation of anti-tumor immunity.

**4.2.2 Rationale for pembrolizumab Dose Selection/ Regimen/ Modification**

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

**Protocol/Amendment No.: 717****4.2.3 Rationale for Endpoints****4.2.3.1 Efficacy Endpoints**

The primary endpoint of this clinical trial is overall response rate according to iRECIST. In the large clinical trials in NSCLC and melanoma despite low objective response rates between 18% and 33%, overall survival improved significantly<sup>7-9</sup>. This is based on the finding that if a response appears, it is a long-lasting response. Consequently, the occurrence of a response is crucial for the further prognosis of a patient. Thus, the overall response rate seems to be a reasonable primary endpoint for this phase II clinical trial. The irradiated tumor lesion(s) will be excluded from the iRECIST evaluation. The response rate according to RECIST 1.1 criteria is a secondary endpoint of the trial. Further secondary endpoints are other parameters of a successful treatment as changes of (not irradiated) target lesion, duration of response, progression-free survival and overall survival.

**4.2.3.2 Safety endpoints**

Another aim of the trial is the assessment of safety and tolerability of the combination of pembrolizumab and radiotherapy. Consequently, this was chosen as a secondary endpoint. It is expected that local radiotherapy with pembrolizumab will not increase toxicity grade 3 or higher according to CTCAE 4.0 compared to the control arm with pembrolizumab only. In an interim analysis of an ongoing trial in which pembrolizumab was combined with chemoradiotherapy for locally advanced head and neck cancer, no increased toxicity was reported<sup>34</sup>. The current trial focuses both on the overall toxicity grade 3 or higher and on some special subsets. Both radiotherapy and pembrolizumab can cause pneumonitis. Consequently, pneumonitis grade 2 and pneumonitis grade 3 or higher will be compared separately in both arms. Pembrolizumab may also increase the severity of radiation dermatitis. Thus, skin toxicity is also evaluated separately as grade 2 toxicity and as grade 3 or higher toxicity in both arms.

**4.2.3.3 Biomarker Research**

See translational research 11.0.

**4.2.4 Risk-benefit analysis**

Currently, first line treatment of recurrent and/ or metastatic HNSCC consists of platinum-based chemotherapy in combination with 5-fluorouracil and cetuximab<sup>1</sup>. In second line therapy taxanes or methotrexate are frequently used. The response rates to these treatments are below 10% and the median overall survival is approximately 7 months<sup>4-6</sup>. In a phase 1 study with pembrolizumab 132 patients were included of whom 81.8% had at least one and 59.2% at least two prior therapies. In these heavily pretreated patients pembrolizumab achieved an overall response rate of 24.8% and further 24.8% had stable disease. The most common adverse events

## Protocol/Amendment No.: 717

(AE) (any grade) were fatigue (15.2%), hypothyroidism (9.1%), decreased appetite (7.6%) and rash (7.6%). Severe adverse (grade 3-5) events appeared in 9.8% of the patients. Thus pembrolizumab seems to be a new effective and safe drug for the treatment of recurrent and/or metastatic HNSCC. The other PD-1 inhibitor Nivolumab already improved significantly OS in second line therapy of metastatic HNSCC in another randomized clinical trial<sup>14</sup>. Clinical trials with the aim of the FDA approval of pembrolizumab in second line therapy are currently ongoing (KEYNOTE-040/NCT02252042 or KEYNOTE-55/NCT02255097).

At ESMO 2018 the results of the randomized phase III KEYNOTE-48 trial (ESMO 2018, LBA8\_PR, Burtneß et al.) were presented for the patients with PD-L1 CPS $\geq$ 1. In this cohort pembrolizumab was superior to standard treatment with platinum-based chemotherapy (EXTREME scheme) regarding overall survival. Furthermore, AEs were much lower in the pembrolizumab group. Consequently, the study protocol was amended (amendment 1), that patients with CPS $\geq$ 1 can be included without prior platinum-based therapy.

In clinical routine radiotherapy is frequently used in patients with symptomatic metastases. Furthermore, radiotherapy is first line treatment for brain metastases, spinal cord compression and bone metastases<sup>35</sup>. Radiotherapy is also safe and effective in the treatment of single lung, liver or adrenal metastases<sup>36-38</sup>. Radiotherapy of metastases in these locations is frequently performed in an oligometastatic situation in order to improve systemic tumor control<sup>39,40</sup>. In this study only metastases that will perspectively require radiation will be treated. These can be either metastases that are highly suspected to cause symptoms in the near future or metastases in an oligometastatic situation in order to improve systemic tumor control. Radiotherapy of brain metastases is not allowed in this study as this frequently requires a different dose or fractionation. In clinical routine radiotherapy is frequently performed during a PD-1 inhibitor treatment e.g. for melanoma or lung cancer without a defined fractionation or timing scheme. So far, no increase of toxicity has been reported. In this study the frequently used and easy to deliver treatment scheme of 12 fractions of 3 Gy will be used. As described in detail above, radiotherapy not only acts locally on the irradiated tumor but can also act systemically, the so called “abscopal effect” of radiotherapy<sup>17</sup>. Especially the predictive marker for anti-PD-1 treatment response PD-L1<sup>25</sup> is increased after radiotherapy<sup>26-28</sup>. In preclinical experiments the combination of local radiotherapy and PD-1/PD-L1 pathway blockade improved systemic tumor control<sup>26,29</sup>. Thus local radiotherapy, acting as *in situ* vaccination is probably able to improve the response rate to pembrolizumab in recurrent and/ or metastatic HNSCC.

## **5.0 METHODOLOGY**

### **5.1 Entry Criteria**

#### **5.1.1 Diagnosis/ Condition for Entry into the Trial**

Patients with recurrent and/ or metastatic HNSCC after progression to first or any second line chemotherapy can be included in this trial.

#### **5.1.2 Subject Inclusion Criteria**

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

1. Be willing and able to provide written informed consent/ assent for the trial.
2. Be  $\geq 18$  years of age on day of signing informed consent.
3. Metastatic HNSCC or metastatic squamous cell CUP (carcinoma of unknown primary) of the neck (at least two distinct lesions: Lesion planned for radiotherapy with  $\geq 2$ ml tumor volume, or  $\geq 3$  lesions: 1 lesion planned for radiotherapy with  $\geq 2$ ml tumor volume or 2 lesions planned for radiotherapy with a cumulative tumor volume  $\geq 2$ ml)

AND/ OR

Locally recurrent HNSCC not suitable for curative local treatment within or outside the previously irradiated tissue (at least two distinct lesions: Lesion planned for radiotherapy with  $\geq 2$  ml tumor volume, or  $\geq 3$  lesions: 1 lesion planned for radiotherapy with  $\geq 2$  ml tumor volume or 2 lesions planned for radiotherapy with a cumulative tumor volume  $\geq 2$ ml).

At least in one of these lesions must be a need for radiotherapy in near future (as defined in inclusion criterion 4).

4. Need for radiotherapy in near future as defined in the following. At least one of the following criteria must be fulfilled:
  - Primary tumor causing mild pain or swallowing problems
  - Lymph node or soft tissue metastasis with distance less than 1 cm to the skin (radiotherapy to prevent weeping tumor infiltration of the skin or fistula)
  - Bone metastases causing mild pain (without risk of fracture)
  - Lung metastases, lymph node metastases, liver metastases or adrenal gland metastases with a diameter above 1 cm in an oligometastatic situation (defined as a maximum of 5 tumor lesions)
  - Lung metastases or mediastinal lymph node metastases causing hemoptysis or permanent severe dry cough

## Protocol/Amendment No.: 717

- Lung metastases or mediastinal lymph node metastases close to trachea or main bronchus (radiotherapy to prevent tumor infiltration and bleeding)
  - Liver metastases causing intrahepatic bile duct obstruction.
5. Progression after first line platinum-based or any second/ third line chemotherapy OR  
Progression within 6 months after platinum-based radiochemotherapy of locally advanced disease  
OR  
First line treatment if PD-L1 CPS (combined positive score)  $\geq 1$ .
6. Histological confirmation of HNSCC or squamous cell CUP (carcinoma of unknown primary) of the neck.
7. Have at least one measurable lesion according to iRECIST that receives less than 10% of the prescribed dose of the irradiated lesion(s) (not considering doses from previous radiotherapy).
8. Have a performance status of 0-1 on the ECOG Performance Scale.
9. Demonstrate adequate organ function as defined in table 2, all screening labs should be performed within 10 days of treatment initiation.

Table 2: Adequate Organ Function Laboratory Values

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelets	$\geq 100,000$ / mcL
Hemoglobin	$\geq 9$ g/dL or $\geq 5.6$ mmol/L without transfusion or EPO dependency (within 7 days of assessment)
<b>Renal</b>	
Serum creatinine <u>OR</u> Measured or calculated <sup>a</sup> creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5$ X upper limit of normal (ULN) <u>OR</u> $\geq 60$ ml/min for subject with creatinine levels $> 1.5$ X institutional ULN
<b>Hepatic</b>	
Serum total bilirubin	$\leq 1.5$ X ULN <u>OR</u> Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5$ ULN
AST (SGOT) and ALT (SGPT)	$\leq 2.5$ X ULN <u>OR</u>

## Protocol/Amendment No.: 717

	≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤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
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
<sup>a</sup> Creatinine clearance should be calculated per institutional standard.	

10. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. A highly sensitive pregnancy test must be used. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential (Section 5.7.2) must be willing to use a highly effective contraceptive measure as defined in the Clinical Trial Facilitation Group (CTFG) guideline (“Recommendations related to contraception and pregnancy testing in clinical trials.”) For details see Section 5.7.2 of the study protocol. Highly effective contraception is required for the course of the study through 120 days after the last dose of study medication.
12. Generative male subjects (Section 5.7.2) must agree to use a highly effective method of contraception as outlined in Section 5.7.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

### 5.1.3 Subject Exclusion Criteria

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

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

**Protocol/Amendment No.: 717**

2. Has need for palliative radiotherapy for symptomatic metastases. This includes the following situations:
- New or progressive central nervous system metastases
  - Metastases causing significant pain
  - Instable bone metastases
  - Lung metastases or mediastinal lymph node metastases with active bleeding

Other metastases that require prompt radiotherapy in the opinion of the investigator.

3. Has only a tumor lesion perspective requiring re-irradiation after prior radiotherapy less than three months ago.
4. 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.
5. Has a known history of active TB (Bacillus Tuberculosis).
6. Hypersensitivity to pembrolizumab or any of its excipients.
7. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study day 1 or who has not recovered (i.e.,  $\leq$  grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier, with the exception of Cetuximab (here only a 2 weeks intermission is required)
8. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or who has not recovered (i.e.,  $\leq$  grade 1 or at baseline) from AEs due to a previously administered agent.
- Note: Subjects with  $\leq$  grade 2 neuropathy are an exception to this criterion and may qualify for the study.
  - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
9. Has known history or concurrent other malignancy. Exceptions include patients, who have been disease free for at least five years. Further exceptions are completely resected basal cell carcinoma or squamous cell carcinoma of the skin or successfully treated in situ carcinoma.
10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided

## Protocol/Amendment No.: 717

- they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
11. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
  12. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
  13. Has an active infection requiring systemic therapy.
  14. 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.
  15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
  16. 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.
  17. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent (One single administration of an anti-PD1, anti-PD-L1 or anti-PD-L2 agent as induction treatment in locally advanced disease is no exclusion criteria).
  18. Has a known history of human immunodeficiency virus (HIV) (HIV ½ antibodies).
  19. Has known active hepatitis B (e.g., HbsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).
  20. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.  
*Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

## Protocol/Amendment No.: 717

21. Have a performance status of  $\geq 2$  on the ECOG Performance Scale.

## 5.2 Trial Treatments

The treatment to be used in this trial is outlined below in table 3

Table 3: Trial Treatment

Drug	Single dose	Frequency / Cumulative dose	Route of Administration	Time schedule	Use
Pembrolizumab	200 mg	Q3W	IV infusion*	Day 3 of radiotherapy (Friday), Q3W	Experimental
Radiotherapy	3Gy	5 days per week / 36Gy	percutaneous	Day 1 on Wednesday	clinical standard for symptomatic tumor lesions and oligometastatic situation

\*Pembrolizumab should be administered as IV infusion over 30 minutes.

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

### 5.2.1 Treatment with pembrolizumab

#### 5.2.1.1 Dose Selection

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

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Investigator's Brochure (IB) for the investigational medicinal product or in the Summary of medicinal Product Characteristics (SmPC) for the authorized product.

### **5.2.1.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy**

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 4.

## Protocol/Amendment No.: 717

Table 4: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

## General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of pneumonitis</li> <li>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment</li> </ul>
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever)</li> </ul>

**Protocol/Amendment No.: 717**

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		<p>and of bowel perforation (ie, peritoneal signs and ileus)</p> <ul style="list-style-type: none"> <li>• Participants with <math>\geq</math>Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis</li> <li>• 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</li> </ul>
AST or ALT Elevation or Increased Bilirubin	Grade 2 <sup>a</sup>	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)</li> </ul>
	Grade 3 <sup>b</sup> or 4 <sup>c</sup>	Permanently discontinue	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia	Withhold <sup>d</sup>	<ul style="list-style-type: none"> <li>• Initiate insulin replacement therapy for participants with T1DM</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for hyperglycemia or other signs and symptoms of diabetes</li> </ul>

**Protocol/Amendment No.: 717**

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	associated with evidence of $\beta$ -cell failure		<ul style="list-style-type: none"> <li>Administer antihyperglycemic in participants with hyperglycemia</li> </ul>	
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids and initiate hormonal replacements as clinically indicated</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>d</sup>		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> <li>Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>d</sup>		
Hypothyroidism	Grade 2, 3 or 4	Continue	<ul style="list-style-type: none"> <li>Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders</li> </ul>
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>Monitor changes of renal function</li> </ul>
	Grade 3 or 4	Permanently discontinue		

## Protocol/Amendment No.: 717

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event <sup>c</sup>		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

**Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.**

<sup>a</sup> AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

<sup>b</sup> AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

**Protocol/Amendment No.: 717**

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
<p><sup>c</sup> AST/ALT: &gt;20.0 x ULN, if baseline normal; &gt;20.0 x baseline, if baseline abnormal; bilirubin: &gt;10.0 x ULN if baseline normal; &gt;10.0 x baseline if baseline abnormal</p> <p><sup>d</sup> The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.</p> <p><sup>e</sup> Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.</p>				

Dosing interruptions are permitted in the case of medical/ surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/ or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

## 5.2.2 Treatment with Radiotherapy

### 5.2.2.1 Technical factors of Radiotherapy

Radiotherapy can be performed as three-dimensional radiotherapy (3D-RT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) or stereotactic radiotherapy (SRT). Megavolt equipment of 6 MeV or 12 MeV is essential. A multi-leaf collimator is necessary to allow customized blocking and intensity modulation, if necessary. The radiotherapy technique is chosen by the treating radiation oncologist depending on the anatomical location of the metastasis.

### 5.2.2.2 Immobilization and planning CT scan

The use of positioning devices depends on the treated anatomical region. Radiotherapy of tumor lesions in the head-and-neck region requires an individual rigid immobilization mask or equal non-rigid immobilization devices. A treatment planning CT scan is essential for defining the target volume. The use of intravenous contrast agent is recommended, but not essential. The CT scan slice thickness should not exceed 5mm. For the CT scan and radiotherapy the patient must be in the same position and use the same immobilization device. All anatomical areas receiving any irradiation must be included in the CT scan. In case of metastases in moving organs as lung or liver, repeated CT scans in the different breathing phases or a 4D-CT scan with a continuous breathing detection has to be performed.

### 5.2.2.3 Target volumes

One, two or three tumor lesions with a total tumor volume of at least 2ml, which can easily be reached, will be irradiated. If possible, the irradiated tumor volume should be  $\geq 5$ ml. Metastases in bones, muscles, subcutaneous tissue, lymphatic nodes, lung, liver or adrenal glands that will perspectively require radiotherapy can be treated. These can be either metastases that are highly suspected to cause symptoms in the near future or metastases in an oligometastatic situation in order to improve systemic tumor control (see definition in inclusion criterion 4). Radiotherapy of other metastases may be possible after consultation of the leading center. Radiotherapy of brain metastases is not allowed in this protocol, as this frequently requires different doses or fractionations. The gross tumor volume (GTV) should be outlined on all appropriate CT slices. If necessary, image fusion of additional imaging (e.g. MRI) should be used. The clinical target volume (CTV) consist of the GTV with a 3 mm anatomically adapted margin not reaching into cavities and uninvolved bony structures. An additional safety margin is required to generate the planning target volume (PTV) depending on the anatomical location, the used immobilization device, respiration induced movements of the CTV, and the employed verification system at the linear accelerator. In most cases, margins of 3-7 mm are adequate. In case of significant respiratory movements of the CTV, an internal target volume (ITV) should be shaped based on a 4D CT to generate the PTV. Alternatively, moving target can be irradiated by using respiratory gating or tracking techniques. Relevant organs at risk are contoured depending on the anatomical region.

## Protocol/Amendment No.: 717

**5.2.2.4 Dose prescription and dose specification of Radiotherapy**

Radiotherapy will be performed conventionally fractionated with daily single doses of 3Gy to 36Gy over approximately two and a half weeks. Radiation dose will be defined at the ICRU 50 reference point. The isodose curve representing the 95% of the prescribed dose must include the entire PTV. Local dose maxima should not exceed 120%.

**5.2.2.5 Dose modification of Radiotherapy**

In this trial radiotherapy is used to induce dying tumor cells acting as in situ vaccination. If any radiotherapy related toxicity greater than grade 2 occurs, radiotherapy is stopped and not continued after toxicity resolved. Pembrolizumab will be continued as usual.

**5.2.2.6 Documentation requirements and portal films**

On the first day of radiotherapy portal image of each field or orthogonal images that localize the isocenter placement must be obtained. Treatment plans with isodoses, dose volume histograms (DVH) of the target volumes and critical risk organs are obligate for planning. Weekly positioning controls of the patients are essential. Image guided radiotherapy (IGRT) with daily positioning controls is possible, but not necessary. Radiotherapy documentation has to be stored for at least 30 years according to the German regulation for radiation protection (Strahlenschutzverordnung, StrlSchV § 85 Abs. 3).

**5.2.2.7 Critical normal structures and adverse events of radiotherapy**

The critical normal structures depend on the anatomical location of the metastasis. In the following the most common AEs are described for different anatomical regions. Acute side effects are usually transient and resolve within a few weeks following radiotherapy:

Table 5: Possible acute adverse effects of radiotherapy (adapted from Wannemacher et al.<sup>41</sup>):

Radiation dermatitis	In the treatment of tumor lesions close to the skin, radiation dermatitis can appear. There is a range from erythema to weeping skin eczema.
Mucositis	Radiotherapy in the head-and-neck region can induce mucositis. A secondary oral thrush is possible.
Dysphagia	Radiotherapy in the head-and-neck mediastinal area can induce dysphagia.
Pneumonitis	Intrathoracic radiotherapy can induce pneumonitis with coughing, dyspnea or fever. A bacterial superinfection is possible.
Diarrhea	Abdominal radiotherapy can induce meteorism and diarrhea. Severe complications as ileus or bowel perforation are extremely rare.
Cystitis	Pelvic radiotherapy can induce cystitis with painful urination.

Chronic AEs may appear later than three months after radiotherapy:

## Protocol/Amendment No.: 717

Table 6: Possible late adverse effects of radiotherapy (adapted from Wannemacher et al.<sup>41</sup>):

Fibrosis	Fibrosis can affect skin, subcutaneous tissue or muscles and lead to limited mobility and loss of strengths.
Pulmonary fibrosis	Pulmonary fibrosis can be a late complication of pneumonitis. Local fibroses are asymptomatic in most of the cases. Severe pulmonary fibroses requiring oxygen therapy are extremely rare.
Lymphedema	After radiotherapy of axillary, cervical or inguinal lymph nodes a lymphedema may appear.
Impaired wound healing	In irradiated areas wound healing can be impaired after injuries or surgical procedures.
Renal insufficiency	Radiotherapy induced renal insufficiency is extremely rare.
Hepatic insufficiency	Hepatic insufficiency after radiotherapy of hepatic metastases is extremely rare.
Bowl stenosis, ileus, fistula	Abdominal radiotherapy can lead to irregular adhesions of intestinal loops. Severe complications as fistula or ileus are extremely rare.
Heart failure, arrhythmia, heart attack	Cardiac complications as heart failure, arrhythmia of heart attack are extremely rare.

Depending on the anatomical region the following dose limits must be respected:

Table 7: Dose limits for critical normal structures (adapted from Wannemacher et al.<sup>41</sup> and Hristow et al.<sup>42</sup> that base on RTOG guidelines). Dose limits were approved by the DEGRO Expertenkommission.

<b>Patients without prior radiotherapy. Dose limits for normal structures for single doses of 2Gy.</b>	
Spinal cord (no previous radiotherapy)	$D_{\max} < 45 \text{ Gy}$
brainstem (no previous radiotherapy)	$D_{\max} < 54 \text{ Gy}$
lung	$V_{20} < 30\%$
liver	$V_{30} < 35\%$
kidney	$V_{18} < 20\%$
<b>Patients without prior radiotherapy. Calculated dose limits for normal structures for single doses of 3Gy. Calculated with a <math>\alpha/\beta</math>-value of 3.</b>	
Spinal cord (no previous radiotherapy)	$D_{\max} < 37,5 \text{ Gy}$
brainstem (no previous radiotherapy)	$D_{\max} < 45 \text{ Gy}$

## Protocol/Amendment No.: 717

lung	$V_{16} < 30\%$	
liver	$V_{25} < 35\%$	
kidney	$V_{15} < 20\%$	
<b>Patients with prior radiotherapy. Dose limits for normal structures for single doses of 2Gy. These dose limits must be adapted for the 3Gy single doses used in the trial and possibly differing single doses of a previous radiotherapy by the treating radiation oncologist. A <math>\alpha/\beta</math>-value of 3 is recommended for the calculations.</b>		
	Interval <6 months:	interval $\geq 6$ months:
Previously irradiated spinal cord	Cumulative $D_{\max} < 54\text{Gy}$	Cumulative $D_{\max} < 60\text{Gy}$
Previously irradiated brainstem	Cumulative $D_{\max} < 54\text{Gy}$	Cumulative $D_{\max} < 60\text{Gy}$
irradiated bones, peripheral nerves, and soft tissues	Cumulative $D_{\max} < 110\text{Gy}$	Cumulative $D_{\max} < 120\text{Gy}$
Previously irradiated lung	Cumulative $V_{20} < 30\%$	
Previously irradiated liver	Cumulative $V_{30} < 35\%$	
Previously irradiated kidney	Cumulative $V_{18} < 20\%$	

### 5.2.3 Adverse events of radiotherapy combined with pembrolizumab

There exist only few clinical studies focusing on the toxicity of the combination of radiotherapy and pembrolizumab. Due to the frequent clinical use of pembrolizumab and palliative radiation therapy in patients with metastatic melanoma and NSCLC outside clinical trials and the lack of reported cases with severe toxicities, this combination seems to be feasible. However, some toxicities are probably increased. The risk of pneumonitis is probably increased in the combination as both intrathoracic radiotherapy and pembrolizumab can induce pneumonitis. In patients with history of prior thoracic radiotherapy pneumonitis occurred more frequently (6.9%) than in patients without prior thoracic radiotherapy (2.9%) (IB edition 15). Furthermore, the risk of diarrhea might be increased if abdominal metastases are irradiated in combination with pembrolizumab. A frequent late toxicity of chemoradiation of locally advanced HNSCC is hypothyroidism<sup>43</sup>. As also pembrolizumab can induce hypothyroidism, the risk is probably increased in patients with history of prior radiotherapy of locally advanced HNSCC. Recently severe skin reactions including Stevens-Johnson syndrome or toxic epidermal necrolysis have been described in patients treated with pembrolizumab. As also radiotherapy can cause radiation dermatitis, the risk could be increased in combined treatment. However, in a recent trial combining chemoradiation of locally advanced HNSCC (radiation dose 70Gy) with pembrolizumab, no increased risk of severe radiation dermatitis was reported<sup>34</sup>.

#### **5.2.4 Timing of Administration of pembrolizumab and Radiotherapy**

Day 1 of the study with the first radiation will always be Wednesday. Pembrolizumab will be administered on day 3 of the study (Friday) after radiotherapy. Radiotherapy is continued the following Monday. This time schedule for radiotherapy and the first pembrolizumab dose must not be changed. Trial treatment should be administered after all procedures/ assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). The following pembrolizumab doses 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 200 mg will be administered as a 30-minute IV infusion every 3 weeks. 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 IB/ SmPC contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

#### **5.2.5 Trial Blinding/ Masking**

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

### **5.3 Randomization or Treatment Allocation**

A written informed consent has to be signed by every patient. A total of 130 patients will be enrolled into the study. All patients fulfilling the inclusion and exclusion criteria will be randomized 1:1 into two groups. Every patient will receive a study number representing the study site and the consecutive number of randomized patients. Patients will be randomized to either arm A (pembrolizumab with radiotherapy) or arm B (pembrolizumab without radiotherapy).

### **5.4 Stratification**

Randomization will be stratified according the following criteria:

**Protocol/Amendment No.: 717**

- Local recurrence versus metastatic disease
- ECOG performance score 0 versus 1

## **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 treatment 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.

### **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 Serious Adverse Events (SAEs) and Events of Clinical Interest (ECIs) as defined in Section 7.2.

### **5.5.2 Prohibited Concomitant Medications/ Therapies**

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Further radiation therapy (If a patient requires radiotherapy without tumor progression according to iRECIST criteria, he must be dropped from the treatment period of the study.)

**Protocol/Amendment No.: 717**

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/ zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from suspected immunological AEs (as defined in Section 5.6.1). 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 abort treatment in this trial. These patients are still included in the statistical analysis (intent-to-treat analysis). Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describe 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 pembrolizumab**

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

**Note:** If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 4 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

Table 8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<b>Grade 1</b>  Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
<b>Grade 2</b>  Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	<p><b>Stop Infusion.</b></p> <p>Additional appropriate medical therapy may include but is not limited to:</p> <p>IV fluids</p> <p>Antihistamines</p> <p>NSAIDs</p> <p>Acetaminophen</p> <p>Narcotics</p> <p>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.</p> <p>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion</p>	<p>Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with:</p> <p>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).</p> <p>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).</p>

**Protocol/Amendment No.: 717**

	<p>rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.</p> <p><b>Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention</b></p>	
<p><b>Grades 3 or 4</b></p> <p>Grade 3:</p> <p>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)</p> <p>Grade 4:</p> <p>Life-threatening; pressor or asectomiz support indicated</p>	<p><b>Stop Infusion.</b></p> <p>Additional appropriate medical therapy may include but is not limited to:</p> <p>Epinephrine**</p> <p>IV fluids</p> <p>Antihistamines</p> <p>NSAIDs</p> <p>Acetaminophen</p> <p>Narcotics</p> <p>Oxygen</p> <p>Pressors</p> <p>Corticosteroids</p>	No subsequent dosing

**Protocol/Amendment No.: 717**

	<p>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.</p> <p>Hospitalization may be indicated.</p> <p><b>**In cases of anaphylaxis, epinephrine should be used immediately.</b></p> <p><b>Participant is permanently discontinued from further study drug intervention.</b></p>	
<p>Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.</p> <p>For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at <a href="http://ctep.cancer.gov">http://ctep.cancer.gov</a></p>		

## 5.6.2 Additional supportive Care Guidelines Radiotherapy

Table 9: Supportive Care Guidelines Radiotherapy

Radiation dermatitis	grade 1: topical (e.g. Dexpanthenol) grade 2: topical (e.g. Polyhexanid) grade 3: topical (e.g. Silver sulfadiazine), consider antibiotics in case of bacterial superinfection
Mucositis	mouth rinsing solutions, consider local fungicides
Dysphagia	sip feed nutrition, analgesics
Pneumonitis	according to supportive care guidelines pembrolizumab, consider antibiotics in case of bacterial superinfection
Diarrhea	according to supportive care guidelines pembrolizumab
Cystitis	consider antibiotics in case of bacterial superinfection

## 5.7 Diet/ Activity/ Other Considerations

### 5.7.1 Diet

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

### 5.7.2 Contraception

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

For this trial, male subjects will be considered to be of non-reproductive potential if they are permanently sterile by bilateral orchidectomy.

Female subjects will be considered of non-reproductive potential if they are either:

postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

**Protocol/Amendment No.: 717**

have had a hysterectomy and/ or bilateral oophorectomy and/ or bilateral salpingectomy, at least 6 weeks prior to screening;

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

practice abstinence<sup>†</sup> from heterosexual activity;

OR

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

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

Methods of contraception for female participants with child bearing potential must be highly effective. The following methods are allowed for female participants in the trial:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- asectomized partner (after medical assessment of surgical success)

For male participants in the trial with women with child bearing potential the following methods of contraception are allowed:

- highly effective method of contraception of the women with child bearing potential (see above)
- bilateral vasectomy (after medical assessment of surgical success)
- Condoms

**Protocol/Amendment No.: 717**

Highly effective contraception is required for the course of the study through 120 days after the last dose of study medication.

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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of initiation of study treatment (or 14 days prior to the initiation of study treatment for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the 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 without delay and within 1 working day to the Sponsor and to MSD Germany Pharmacovigilance (Email: [arzneimittelsicherheit@msd.de](mailto:arzneimittelsicherheit@msd.de), backup for fax: +49 89 / 456 11352) 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 MSD Germany Pharmacovigilance (Email: [arzneimittelsicherheit@msd.de](mailto:arzneimittelsicherheit@msd.de), backup for fax: +49 89 / 456 11352) 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 discontinue trial treatment 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 7.1.2.7.

- 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 12 months of uninterrupted treatment with pembrolizumab

*Note:* 12 months of study medication is calculated from the date of first dose.

- 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 AE monitoring (SAEs will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than 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

**Protocol/Amendment No.: 717**

for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

### **5.8.1 Discontinuation of Study Treatment after CR**

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR according to iRECIST was declared.

### **5.9 Subject Replacement Strategy**

No subject replacement is planned in this trial.

### **5.10 End of the trial**

The trial ends when the last patient completes the safety follow-up visit. Patients continue receiving Pembrolizumab for up to 1 year outside of the trial, which meets the general admission in this clinical indication.

### **5.11 Clinical Criteria for Early Trial Termination**

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

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

In the event of MSD 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	Treatment Phase			Treatment outside of trial <i>According to guidelines</i>				End of Treatment <i>According to guidelines</i>	Post-Treatment <i>According to guidelines</i>	
Treatment Cycle <sup>m</sup> /Title:		1 (doses 1 & 2)	Last RT	Safety Follow-up	To be repeated beyond 4 cycles				Discontinuation <sup>b</sup>	Follow Up Visits <sup>c</sup>	Survival Follow-Up <sup>d</sup>
					1 (doses 3-4)	2	3	4			
Scheduling Window (Days):	-28 to -1 <sup>g</sup>			30 days post dose 2	± 3	± 3	± 3	± 3	At time of discon.	Every 12 weeks post discon.	Every 12 weeks
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X			X	X	X	X			

## Protocol/Amendment No.: 717

Trial Period	Screening Phase	Treatment Phase			Treatment outside of trial <i>According to guidelines</i>				End of Treatment <i>According to guidelines</i>	Post-Treatment <i>According to guidelines</i>	
Treatment Cycle <sup>m</sup> /Title:		1 (doses 1 & 2)	Last RT	Safety Follow-up	To be repeated beyond 4 cycles				Discontinuation <sup>b</sup>	Follow Up Visits <sup>c</sup>	Survival Follow-Up <sup>d</sup>
					1 (doses 3-4)	2	3	4			
Scheduling Window (Days):	-28 to -1 <sup>g</sup>			30 days post dose 2	± 3	± 3	± 3	± 3	At time of discon.	Every 12 weeks post discon.	Every 12 weeks
Post-study anticancer therapy status				X						X	
Survival Status											X
Review AEs	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X		X	X							
Directed Physical Examination		X			X	X	X	X	X		
Vital Signs and Weight	X	X		X	X	X	X	X	X		
12-lead ECG	X			X							
ECOG Performance Status	X	X		X	X	X	X	X	X		

## Protocol/Amendment No.: 717

Trial Period	Screening Phase	Treatment Phase			Treatment outside of trial <i>According to guidelines</i>				End of Treatment <i>According to guidelines</i>	Post-Treatment <i>According to guidelines</i>	
Treatment Cycle <sup>m</sup> /Title:		1 (doses 1 & 2)	Last RT	Safety Follow-up	To be repeated beyond 4 cycles				Discontinuation <sup>b</sup>	Follow Up Visits <sup>c</sup>	Survival Follow-Up <sup>d</sup>
					1 (doses 3-4)	2	3	4			
Scheduling Window (Days):	-28 to -1 <sup>g</sup>			30 days post dose 2	± 3	± 3	± 3	± 3	At time of discon.	Every 12 weeks post discon.	Every 12 weeks
Pregnancy Test – Urine or Serum β HCG	X <sup>h</sup>			X				X			
HIV, Hepatitis B/C test	X <sup>k</sup>										
PT/INR and aPTT	X <sup>k</sup>										
CBC <sup>k</sup>	X <sup>e, k</sup>	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel	X <sup>k</sup>	X	X	X	X	X	X	X	X		
Urinalysis	X <sup>k</sup>			X							
FT3, FT4 and TSH	X <sup>k</sup>			X				X			
Tumor Imaging <sup>f</sup>	X				X	X	X	X		X	

## Protocol/Amendment No.: 717

Trial Period	Screening Phase	Treatment Phase			Treatment outside of trial <i>According to guidelines</i>				End of Treatment <i>According to guidelines</i>	Post-Treatment <i>According to guidelines</i>	
Treatment Cycle <sup>m</sup> /Title:		1 (doses 1 & 2)	Last RT	Safety Follow-up	To be repeated beyond 4 cycles				Discontinuation <sup>b</sup>	Follow Up Visits <sup>c</sup>	Survival Follow-Up <sup>d</sup>
					1 (doses 3-4)	2	3	4			
Scheduling Window (Days):	-28 to -1 <sup>g</sup>			30 days post dose 2	± 3	± 3	± 3	± 3	At time of discon.	Every 12 weeks post discon.	Every 12 weeks
Archival Tissue Collection	X										
Correlative Studies Blood Collection	X <sup>a</sup>	X		X	X <sup>a</sup>	X <sup>a</sup>	X <sup>a</sup>				
Patient questionnaires	X				X <sup>l</sup>	X <sup>l</sup>					

## Protocol/Amendment No.: 717

Trial Period	Screening Phase	Treatment Phase			Treatment outside of trial <i>According to guidelines</i>				End of Treatment <i>According to guidelines</i>	Post-Treatment <i>According to guidelines</i>	
Treatment Cycle <sup>m</sup> /Title:		1 (doses 1 & 2)	Last RT	Safety Follow-up	To be repeated beyond 4 cycles				Discontinuation <sup>b</sup>	Follow Up Visits <sup>c</sup>	Survival Follow-Up <sup>d</sup>
					1 (doses 3-4)	2	3	4			
Scheduling Window (Days):	-28 to -1 <sup>g</sup>			30 days post dose 2	± 3	± 3	± 3	± 3	At time of discon.	Every 12 weeks post discon.	Every 12 weeks

<sup>a</sup> at screening only for patients in treatment arm A (with RT); treatment cycles (only at doses P2, P3, P4, P8, P12): correlative study blood has to be collected before study treatment; a maximum of 8 samples will be collected  
<sup>b</sup> Discontinuation after unacceptable toxicity, tumor progression, patient's wish or last dose of Pembrolizumab  
<sup>c</sup> if no tumor progression appeared  
<sup>d</sup> after tumor progression  
<sup>e</sup> with differential CBC  
<sup>f</sup> CT neck-thorax-abdomen (additional MRI of the brain if stable brain metastases have been diagnosed prior treatment), at doses P4, P7, P10, P13, P16  
<sup>g</sup> the screening phase can be prolonged for 7 days for radiotherapy treatment planning after consultation of the leading center  
<sup>h</sup> after informed consent of the patient in women with child bearing potential within 72 hours prior to the first dose of treatment  
<sup>k</sup> to be performed within 10 days prior to the first dose of treatment  
<sup>l</sup> only before third and seventh pembrolizumab administration  
<sup>m</sup> one cycle consists of 12 weeks with a maximum of 4 Pembrolizumab doses

**Protocol/Amendment No.: 717**

## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

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

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

#### **7.1.1 Administrative Procedures**

##### **7.1.1.1 Informed Consent**

The investigator must obtain documented consent from each potential subject 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.

**Protocol/Amendment No.: 717**

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 Demographics and 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. Furthermore, demographics including smoking have to be recorded. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

**7.1.1.4 Prior and Concomitant Medications Review**

**7.1.1.4.1 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 trial treatment. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

**7.1.1.4.2 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.

**7.1.1.5 Disease Details and Treatments**

**7.1.1.5.1 Disease Details**

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

**7.1.1.5.2 Prior Treatment Details**

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

**Protocol/Amendment No.: 717**

**7.1.1.5.3 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 End of Treatment 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.

**7.1.1.6 Assignment of Screening Number**

The screening number will be assigned to the patient after the pre-screening by consecutive numbers at every center. On the screening form in the ISF it has to be documented:

- date of written informed consent

AND

If the patient was randomized:

- Study number of the patient assigned by the randomization service
- Date of randomization

If the patient was not randomized:

- Reason for Not-Randomization

**7.1.1.7 Assignment of Randomization Number**

Subjects fulfilling all in-/ exclusion criteria, having provided written informed consent on the approved informed consent form, are eligible for participation in the study.

Enrollment/ randomization is performed in secuTrial®. The following data must be provided:

- Access code of person performing the randomization
- Month/ year of patient's birth
- Sex of patient
- Date of written informed consent
- Stratification criteria

The randomization result (patient no. and treatment allocation) is displayed online immediately. Furthermore, an email will be sent to defined persons that need to know about the randomization.

**Protocol/Amendment No.: 717**

In case of technical problems or questions, please contact the study office at the leading center by email or phone.

## **7.1.2 Clinical Procedures/ Assessments**

### **7.1.2.1 Adverse Event (AE) Monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart (Section 6.0) 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 4.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

### **7.1.2.2 Full Physical Examination**

The investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening, after the last dose of radiotherapy and in the Safety Follow-up Visit.

### **7.1.2.3 Directed Physical Examination**

For cycles that do not require a full physical examination per the Trial Flow Chart (Section 6.0), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. A directed physical examination will also be performed at the End of Treatment Visit.

### **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, at treatment discontinuation and in the Safety Follow-up Visit 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 Electrocardiogram**

A 12-lead ECG will be performed in the screening phase and in the Safety Follow-up Visit.

**Protocol/Amendment No.: 717**

**7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale**

The investigator or qualified designee will assess ECOG status (see Section 14.1) at screening, prior to the administration of each dose of trial treatment, at discontinuation of trial treatment and in the Safety Follow-up Visit as specified in the Trial Flow Chart (Section 6.0).

**7.1.2.7 Tumor Imaging and Assessment of Disease**

Tumor imaging will be performed with a CT scan of the neck, thorax and abdomen. Contrast agent should be used unless renal function is substantially reduced or a present manifest hyperthyroidism is diagnosed. In patients with stable brain metastases prior treatment, an additional MRT-scan of the brain is necessary. Tumor imaging will be evaluated according to RECIST and iRECIST at the University Hospital Erlangen for all patients. Treatment duration of pembrolizumab bases on iRECIST criteria. During the treatment period, imaging will be performed every nine weeks or if a tumor progression is clinically suspected. In case of an unconfirmed progressive disease, the following imaging can be performed earlier (minimum time interval of 4 weeks). During the Follow-up, imaging will be performed every twelve weeks or if a tumor progression is clinically suspected.

**7.1.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling**

Tumor tissue will be collected by the Department of Pathology of the University Hospital Erlangen. The most recent achieved tissue sample will be requested from the local pathologist. Blood samples for the characterization of the immune status of the peripheral blood should be drawn during the Screening phase only for patients in treatment arm A (with radiotherapy) and prior to the first four administrations of pembrolizumab. Afterward blood samples will be drawn prior to the eighth and twelfth pembrolizumab administrations. One further blood sample should be drawn in the Safety Follow-up Visit. A maximum of eight samples will be collected. The blood samples will be collected in the Laboratory for Radiation-Immunobiology Erlangen.

**7.1.3 Laboratory Procedures/ Assessments**

Details regarding specific laboratory procedures/ assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 10.

Table 10: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	( $\beta$ -hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam ( <i>If abnormal</i> )	Free triiodothyronine (FT3)
ANC	Uric Acid		Free tyroxine (FT4)
Absolute Lymphocyte Count	Calcium	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Chloride		
	Glucose		
	Phosphorus		Blood for correlative studies
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin ( <i>If total bilirubin is elevated above the upper limit of normal</i> )		
	Total protein		
	Blood Urea Nitrogen		

† in women with child bearing potential within 72 hours prior to the first dose of treatment

**Protocol/Amendment No.: 717**

Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 3 days 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.

#### **7.1.4 Other Procedures**

##### **7.1.4.1 Withdrawal/ Discontinuation from study**

If a subject discontinues/ withdraws from study during the treatment period, all applicable activities scheduled for the End of Treatment Visit should be performed. Any AEs which are present at the time of discontinuation/ withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 – Assessing and Recording Adverse Events. After discontinuing treatment, subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.4.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4.2 and 7.1.5.4.3).

If a patient withdraws from study during the follow up period, all procedures for the current follow up visit should be performed.

##### **7.1.4.2 Blinding/ Unblinding**

The study is performed open-label. There will be no blinding.

##### **7.1.4.3 Patient questionnaires**

Quality of life will be measured with the EORTC QLQ-C30 and EQ-5D-5L questionnaires during Screening and before the fourth and seventh application of pembrolizumab.

#### **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**

The screening investigations should be performed 28 to 1 day prior to the begin of radiotherapy or the administration of the first dose of pembrolizumab. In case of a required radiotherapy treatment planning the screening phase can be prolonged for 7 days after consultation of the leading center. Laboratory tests for screening should be performed within 10 days prior to the administration of the first dose of treatment. For women of child bearing potential a highly

**Protocol/Amendment No.: 717**

sensitive pregnancy test should be performed within 72 hours prior to the first dose of treatment. Achieved tumor tissue for correlative studies is collected after informed consent of the patient.

**7.1.5.2 Treatment Period**

Treatment within the trial is finalized when the Safety Follow-Up visit is performed after administration of two doses of Pembrolizumab.

Treatment in group A (with radiotherapy) starts with the first radiation on a Wednesday. The first pembrolizumab dose will be administered after the third radiation on Friday. After the last dose of radiotherapy, a full physical examination is required to detect all AEs. Furthermore, concomitant medication must be revised and a CBC and a comprehensive serum chemistry panel is required.

In group B treatment comprises two doses of pembrolizumab followed by the Safety Follow-Up.

It is recommended to continue treatment with Pembrolizumab up to 1 year after start of treatment (Arm A and B). Pembrolizumab outside of the trial will be continued as usual every third week. Before every administration of pembrolizumab concomitant medication and AEs must be revised and vital signs, weight and ECOG have to be documented. Furthermore, a CBC and a comprehensive serum chemistry panel is required prior every administration of pembrolizumab.

In both groups (A and B), tumor imaging with CT Neck-Thorax-Abdomen is performed every 9 weeks. At these time points also a highly sensitive pregnancy test should be performed in women with child bearing potential. In case of stable brain metastases an additional MRI of the brain is required. Treatment is continued till unacceptable toxicity, tumor progression according to iRECIST criteria or patient's wish to end treatment.

As the trial includes patients with metastases perspective requiring radiation, a patient may develop symptoms from a metastasis during the treatment period. If such a patient has no tumor progression according to iRECIST criteria, but requires palliative radiotherapy, he/ she must be dropped from the treatment period of the study. Thereafter a palliative radiotherapy can be done.

**7.1.5.3 End of Treatment Visit**

For all patients who discontinue/ withdraw from treatment or complete the treatment (including treatment with Pembrolizumab outside of the trial), the End of Treatment Visit should be conducted if the withdrawal/ completion does not coincide with an administration of pembrolizumab. AEs and concomitant medications must be revised and vital signs, weight and

**Protocol/Amendment No.: 717**

ECOG have to be documented. Furthermore, a CBC and a comprehensive serum chemistry panel is required.

**7.1.5.4 Post-Treatment Visits****7.1.5.4.1 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 within the trial or before initiation of a new anti-cancer treatment should also be followed and recorded. Concomitant medication must be revised and a full physical examination and a 12-lead ECG have to be performed. Furthermore, the post-study anticancer therapy status should be recorded as well as vital signs, weight and ECOG performance status are required. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 10 (including a highly sensitive pregnancy test in women with child bearing potential).

**7.1.5.4.2 Follow-up Visits**

Follow-Up visits will be performed outside of the trial. Subjects will be seen within the follow-up care in accordance with the guidelines. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks 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 or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. Follow-up Visits will be conducted up to 24 months after the last study treatment.

**7.1.5.4.3 Survival Follow-up**

Survival Follow-Up visits will be performed outside of the trial. Subjects will be seen within the follow-up care in accordance with the guidelines. 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. Survival Follow-up Visits will be conducted up to 24 months after the last study treatment.

**7.1.5.5 Aftertreatment**

Subjects who had no progression of disease and no unacceptable toxicity during the usual treatment period of the trial and are eligible for additional pembrolizumab therapy can be

**Protocol/Amendment No.: 717**

treated with commercially available pembrolizumab. The investigator will prescribe pembrolizumab after evaluation of the individual medical patient need for the treatment with pembrolizumab. The data retrieved during the treatment will be properly captured in electronic case record forms (eCRF) and in the subject's medical records until the last administration of pembrolizumab. Subjects who continue treatment will be treated at the same dose and dose interval as when they last received pembrolizumab until confirmed disease progression according to iRECIST criteria, unacceptable toxicity or patient's wish to stop therapy and will proceed with Post-Treatment visits.

## **7.2 Assessing and Recording Adverse Events**

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

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

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

AEs may occur during the course of the use of MSD product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study and resulting symptoms are not considered AEs.

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

From the time of treatment allocation/ randomization through 30 days following cessation of treatment, all AEs must be reported by the investigator. Such events will be recorded at each

**Protocol/Amendment No.: 717**

examination on the AE case report forms/ worksheets. The reporting timeframe for AEs meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious AEs for outcome.

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

### **7.2.1 Definition of an Overdose for this Protocol and Reporting of Overdose**

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater ( $\geq 5$  times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE is associated with (“results from”) the overdose of a MSD product, the AE is reported as a SAE, even if no other seriousness criteria are met.

If a dose of MSD 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 AE are to be forwarded within 1 working day to the Sponsor, Winicker Norimed and MSD. The report will be made by recording the necessary information in secuTrial®. In the event that the system is unavailable, the Event Reporting Form provided should be completed and submitted to Winicker Norimed (fax: +49 911 / 9260 80 4444, backup for Email: [safety@winicker-norimed.com](mailto:safety@winicker-norimed.com)) either by electronic or paper media. In this case, the reports will be forwarded to the Sponsor and MSD Germany Pharmacovigilance (Email: [arzneimittelsicherheit@msd.de](mailto:arzneimittelsicherheit@msd.de), backup for fax: +49 89 / 456 11352) within 1 working day by Winicker Norimed.

Once secuTrial® is available, all information will need to be entered and submitted via the system.

## **7.2.2 Reporting of Pregnancy and Lactation**

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

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

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

Such events are to be forwarded within 1 working day to the Sponsor, Winicker Norimed and MSD. The report will be made by recording the necessary information in secuTrial®. In the event that the system is unavailable, the Event Reporting Form provided should be completed and submitted to Winicker Norimed (fax: +49 911 / 9260 80 4444, backup for Email: [safety@winicker-norimed.com](mailto:safety@winicker-norimed.com)) either by electronic or paper media. In this case the reports will be forwarded to the Sponsor and MSD Germany Pharmacovigilance (Email: [arzneimittelsicherheit@msd.de](mailto:arzneimittelsicherheit@msd.de), backup for fax: +49 89 / 456 11352) within 1 working day by Winicker Norimed.

Once secuTrial® is available, all information will need to be entered and submitted via the system.

## **7.2.3 Immediate Reporting of Adverse Events**

### **7.2.3.1 Serious Adverse Events**

A serious adverse event (SAE) is any AE occurring at any dose or during any use of MSD 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;

## Protocol/Amendment No.: 717

- Is another important medical event
- **Note:** In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to MSD in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by MSD for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

Refer to Table 11 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/ randomization, any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 1 working day as described below if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/ randomization through **90 days following cessation of treatment**, or **30 days following cessation of treatment if the subject initiates new anticancer therapy**, whichever is earlier, any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the MSD product, must be reported within 1 working day as described below.

Additionally, any SAE, considered by an investigator who is a qualified physician to be related to MSD product that is brought to the attention of the investigator at any time following consent through the end of the specified Safety Follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported within 1 working day.

All subjects with SAEs must be followed up for outcome.

**SAE reports and any other relevant safety information are to be forwarded within 1 working day to the Sponsor, Winicker Norimed and MSD.**

**The report will be made by recording the necessary information in secuTrial®. In the event that the system is unavailable, the SAE Reporting Form provided should be completed and submitted to Winicker Norimed (fax: +49 911 / 9260 80 4444, backup for Email: [safety@winicker-norimed.com](mailto:safety@winicker-norimed.com)) either by electronic or paper media. In this case, the reports will be forwarded to the Sponsor and MSD Germany Pharmacovigilance (Email:**

**Protocol/Amendment No.: 717**

[arzneimittelsicherheit@msd.de](mailto:arzneimittelsicherheit@msd.de), backup for fax: +49 89 / 456 11352) within 1 working day by Winicker Norimed.

**Once secuTrial® is available, all information will need to be entered and submitted via the system.**

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 MSD Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to MSD Germany Pharmacovigilance (Email: [arzneimittelsicherheit@msd.de](mailto:arzneimittelsicherheit@msd.de), backup for fax: +49 89 / 456 11352).

### **7.2.3.2 Events of Clinical Interest**

Selected non-serious and SAEs are also known as Events of Clinical Interest (ECI) and must be reported within 1 working day as described below.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 1 working day as described below if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/ randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to MSD product, must be reported within 1 working day to Winicker Norimed.

Events of clinical interest for this trial include:

1. an overdose of MSD 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.

**Protocol/Amendment No.: 717**

Events of clinical interests are to be forwarded within 1 working day to the Sponsor, Winicker Norimed and MSD. The report will be made by recording the necessary information in secuTrial®. In the event that the system is unavailable, the Event Reporting Form provided should be completed and submitted to Winicker Norimed (fax: +49 911 / 9260 80 4444, backup for Email: [safety@winicker-norimed.com](mailto:safety@winicker-norimed.com)) either by electronic or paper media. In this case the reports will be forwarded to the Sponsor and MSD Germany Pharmacovigilance (Email: [arzneimittelsicherheit@msd.de](mailto:arzneimittelsicherheit@msd.de), backup for fax: +49 89 / 456 11352) within 1 working day by Winicker Norimed.

Once secuTrial® is available, all information will need to be entered and submitted via the system.

### **7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting**

Efficacy endpoints as outlined in this section will not be reported as described in Section 7.2.3. Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

### **7.2.4 Evaluating Adverse Events**

An investigator who is a qualified physician will evaluate all AEs according to CTCAE 4.0. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE case report forms/ worksheets.

All AEs regardless of CTCAE grade must also be evaluated for seriousness and relationship to MSD product or radiotherapy (if applicable).

Table 11: Evaluating AEs

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

<b>V4.0 CTCAE Grading</b>	<b>Grade 1</b>	<b>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</b>
	<b>Grade 2</b>	<b>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).</b>
	<b>Grade 3</b>	<b>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.</b>
	<b>Grade 4</b>	<b>Life threatening consequences; urgent intervention indicated.</b>
	<b>Grade 5</b>	<b>Death related to AE.</b>
<b>Seriousness</b>	A SAE is any AE occurring at any dose or during any use of MSD & Co., Inc., Kenilworth, New Jersey, U.S.A. product that:	
	† <b>Results in death</b> ; or	
	† <b>Is life threatening</b> ; 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 AE that, had it occurred in a more severe form, might have caused death.); or	
	† <b>Results in a persistent or significant disability/ incapacity</b> (substantial disruption of one's ability to conduct normal life functions); or	

## Protocol/Amendment No.: 717

	<p>†<b>Results in or prolongs an existing inpatient hospitalization</b> (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a MSD product and is documented in the patient's medical history.); or</p> <p>†<b>Is a congenital anomaly/ birth defect</b> (in offspring of subject taking the product regardless of time to diagnosis); or</p> <p><b>Is a new cancer</b> (that is not a condition of the study) (although not serious per ICH definition, is reportable to the Sponsor, Winicker Norimed and MSD within 1 working day to meet certain local requirements); or</p> <p><b>Is an overdose</b> (whether accidental or intentional). Any AE associated with an overdose is considered a SAE for collection purposes. An overdose that is not associated with an AE is considered a non-serious event of clinical interest and must be reported within 1 working day to the Sponsor, Winicker Norimed and MSD.</p> <p><b>Other important medical events</b> that may not result in death, not be life threatening, or not require hospitalization may be considered a SAE 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 †).</p>
<b>Duration</b>	Record the start and stop dates of the AE. If less than 1 day, indicate the appropriate length of time and units
<b>Action taken</b>	Did the AE cause MSD product or radiotherapy to be discontinued?
<b>Relationship to MSD Product</b>	Did MSD product cause the AE? The determination of the likelihood that MSD product caused the AE 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.

**Protocol/Amendment No.: 717**

<p>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 AE based upon the available information.</p> <p><b>The following components are to be used to assess the relationship between MSD product and the AE;</b> the greater the correlation with the components and their respective elements (in number and/ or intensity), the more likely MSD product caused the AE:</p>	
<b>Exposure</b>	Is there evidence that the subject was actually exposed to MSD product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/ metabolite in bodily specimen?
<b>Time Course</b>	Did the AE follow in a reasonable temporal sequence from administration of MSD product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
<b>Likely Cause</b>	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 MSD	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
Product (continued)	<b>Dechallenge</b>	<p>Was MSD product discontinued or dose/ exposure/ frequency reduced?</p> <p>If yes, did the AE resolve or improve?</p> <p>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.</p> <p>(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/ improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/ are only used one time.)</p>
	<b>Rechallenge</b>	<p>Was the subject re-exposed to MSD product in this study?</p> <p>If yes, did the AE recur or worsen?</p> <p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p> <p>(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time).</p> <p>NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MSD PRODUCT, OR IF REEXPOSURE TO MSD PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.</p>
	<b>Consistency with Trial Treatment Profile</b>	<p>Is the clinical/ pathological presentation of the AE consistent with previous knowledge regarding MSD product or drug class pharmacology or toxicology?</p>

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.	
<b>Record one of the following</b>	<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of MSD product relationship).</b>
<b>Yes, there is a reasonable possibility of MSD product relationship.</b>	There is evidence of exposure to MSD product. The temporal sequence of the AE onset relative to the administration of MSD product is reasonable. The AE is more likely explained by MSD product than by another cause.
<b>No, there is not a reasonable possibility of MSD product relationship</b>	Subject did not receive the MSD product OR temporal sequence of the AE onset relative to administration of MSD product is not reasonable OR the AE is more likely explained by another cause than the MSD product. (Also entered for a subject with overdose without an associated AE.)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction, which is suspected, serious and unexpected because the nature or severity of this event is not consistent with the applicable product information (e.g. SmPC for the authorized product or IB for the investigational medicinal product).

**Protocol/Amendment No.: 717**

### **7.2.5 Sponsor Responsibility for Evaluating and Reporting Adverse Events**

In addition to the first evaluation of AEs that is performed by the investigator, a second evaluation with respect to seriousness, causality and expectedness and a risk-benefit assessment is performed by the Sponsor.

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

SUSARs will be reported to IRB/ IECs and competent authorities by Winicker Norimed as follows:

- Non-fatal and non-life-threatening SUSARs latest within 15 calendar days
- Fatal or life-threatening SUSARs latest within seven calendar days

All involved investigators will also be informed by Winicker Norimed.

Furthermore, an Annual Safety Report will be provided to IRB/ IECs and competent authorities by the Sponsor once a year or on request. This task maybe delegated to Winicker Norimed.

As Reference Safety Information either the IB for unauthorized investigational medicinal product or the SmPC for the authorized product will be used.

### **7.2.6 Data Safety Monitoring Committee (DSMC)**

A DSMC will be established to review accumulating safety data during the course of the trial. The DSMC may recommend discontinuation of the trial or modification of the protocol for safety reasons at any time during the trial. The decision to terminate is taken by the sponsor together with the coordinating investigator. The members of the DSMC will be chosen from different fields. The members will not be involved in the design of the study, its conduct other than through their role on the DSMC and will have no financial interest in the outcome of the study. The DSMC will have written operating procedures.

## **8.0 STATISTICAL ASPECTS**

### **8.1 Trial design and primary hypotheses**

The objective of this exploratory randomized phase II study is to obtain some evidence of a superior efficacy of pembrolizumab when combined with local radiotherapy, compared to pembrolizumab alone. Accordingly, the research hypothesis of the study is one-sided. The primary efficacy endpoint is the rate of patients achieving CR or PR as best response during/after treatment (ORR). Thus, the following hypotheses will be tested:

**Protocol/Amendment No.: 717**

$H_0$ : ORR (radiotherapy)  $\leq$  ORR (control)

$H_1$ : ORR (radiotherapy)  $>$  ORR (control)

According to these hypotheses, the test concerning the primary endpoint will be performed one-sided.

## **8.2 Sample size calculation**

Based on published results, the ORR after standard pembrolizumab therapy is assumed to be around 18%. The doubling of this ORR to 36% by adding radiotherapy seems to be a reasonable aim, and is unequivocally considered to be a major, clinically relevant advantage. In order not to miss such a distinct signal for improvement by the experimental treatment (if it actually exists) with a high level of confidence (power = 80%), 65 evaluable patients per arm, i.e. a total of  $n = 130$ , have to be observed, based on an alpha error rate of 0.1 (one-sided). The comparatively high alpha error level of 10% is acceptable within the framework of a phase II study<sup>44-46</sup>.

## **8.3 Evaluation categories of patients**

The primary population for the analyses consists of all randomized patients (intent-to-treat). However, patients who were enrolled although they unequivocally did not fulfil major selection criteria of the trial a priori “non-eligible”), will be excluded from the statistical analysis, in accordance with ICH recommendations. Only case reports will be provided for this group. The decision on exclusions will be made by the steering committee during a pre-analysis meeting in a blinded fashion.

In the pre-analysis meeting, a per-protocol population will likewise be prospectively defined for sensitivity analyses, based on the amount of protocol treatment actually received.

The population for safety analyses consists of all patients having received at least one application of protocol therapy.

Eligible patients without any valid restaging procedure according to iRECIST are counted as failures in the primary analysis.

## **8.4 Methods of statistical analysis**

The primary end-point of the trial (ORR) will be analysed confirmatively by Fisher's exact test considering a level of  $p < 0.1$  (one-sided) as significant.

All other parameters will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/ or confidence intervals (CI). If additional p values are calculated, they will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error. All p values will be two-sided if not stated otherwise. The statistical methods described in this section are suited for the data and distributions usually expected in this type of trials. The suitability will be checked after data entry. If necessary, the statistical method will be modified accordingly and the results of original and modified analyses compared and strictly discussed.

Demographic and prognostic baseline data will be checked for homogeneity between the study arms. In case of relevant imbalances of other important prognostic factors the statistical method may be adjusted in order to achieve best possible comparability of the groups, and the results will be critically reviewed in comparison to the unadjusted ones.

Metric changes in (non-irradiated) target lesions will eventually be compared using the Wilcoxon rank sum test. Secondary endpoints of time-to-event type, such as duration of response, progression-free survival and overall survival, will be estimated according to Kaplan-Meier, and exploratively compared using the logrank test (PETO, 1972, 1977), stratified according to the protocol-defined strata. Hazard ratios (with Cis) will be derived from corresponding Cox proportional hazard models, eventually adjusting for important prognostic factors (sensitivity analysis).

If the Peto logrank test is not appropriate because of violation of the proportional hazard assumption (HAYBITTLE 1988), Gehan's generalization of the Wilcoxon rank sum test for censored data (GEHAN 1965) may be applied, preferably in its modification by PETO (1972) and PRENTICE (1978), as a sensitivity analysis.

Comparisons of the categorical data will be performed using  $\chi^2$  tests, Fisher's exact test or trend tests according to Cochran/Armitage, as appropriate.

No interim analyses for efficacy will be performed.

## 8.5 Statistical Analysis Plan

Further details on the biostatistical methods will be described in a statistical analysis plan (SAP), to be written and approved by the steering committee of the study, prior to locking the data base and before any analyses on efficacy items are performed.

## 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 MSD as summarized in Table 12.

Table 12: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4ml	Solution for Injection

### 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.

**Protocol/Amendment No.: 717**

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 MSD 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**

The investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with Good Clinical Practice (GCP) and local regulations.

The investigator must ensure that the subject's pseudonymity is maintained. On the CRF or other documents submitted to the Sponsor and/ or agent, subjects should be identified by a unique subject identifier as designated by the sponsor.

In compliance with Federal regulations/ ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/ her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

### **10.2 Compliance with Financial Disclosure Requirements**

All investigators have to sign a financial disclosure.

### **10.3 Compliance with Law, Audit and Debarment**

To conduct the study as outlined in the protocol and in compliance with GCP and with applicable regulatory requirements.

### **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**

In addition to the initial visit for site-initiation, the monitor will contact and visit the investigator periodically to evaluate the study progress and the compliance of the study site with GCP, regulations and the study protocol as well as to verify and collect data reported in the eCRF. The investigator as well as any study staff member will cooperate with the monitor to ensure that any problem that may be identified is resolved. The investigator will make all study-related source data and documents available to the monitor or a quality assurance auditor mandated by the Sponsor, or to domestic or foreign regulatory inspectors, after appropriate notification.

### **10.6 Data Management and Data Archiving**

All patient-related data are recorded in a pseudonymized way. Each patient is unequivocally identified by a trial subject number, attributed after randomization into the study. The investigator has to keep a patient identification log, including the full name and address of the subject and possibly additional relevant personal data such as hospital record number, home physician etc. Any patients, including those who were screened in order to be entered into the study, but who could not be recruited for whatever reason (i.e. not fulfilling selection criteria etc.) are recorded in a “patient screening log”.

All the data retrieved during the conduct of the study are entered into the appropriate eCRF by the investigator or another person authorized by the investigator. The access to the eCRFs is provided by the Sponsor and is explained to the investigator by the study monitor.

**Protocol/Amendment No.: 717**

All recorded data have to be plausible and complete. Please respect the following technical details when using the eCRFs:

- All data fields have to be filled, except for those referring to open questions. If a specific test was not performed or an information item is definitely not available or applicable, information on this should be provided (not done = ND, not applicable = NA, unknown = UK). Exception: If a patient discontinues/ withdraws from study treatment earlier than 12 month, not applicable pembrolizumab trial visits in the eCRF must not be completed.
- If a value or date is not known exactly, please explain in the comment field.
- Screening Failures will not be entered in to the eCRF.

The investigator is obliged to complete the case report forms within a reasonable time period after retrieval of the data (i.e. usually within 2 weeks). The study office or monitor checks the forms for completeness and plausibility. In case of queries the monitor fills out the query field. The investigator or a delegated person is responsible for clarification/ correction/ completion. Queries have to be handled within 4 weeks.

After finalization of the data checks by the study office/ monitor the file or the database is closed.

All relevant study documents including the eCRFs are stored at the office of the coordinating investigator/ sponsor for at least 10 years after completion of the final study report. The investigators have to archive major administrative documents (correspondence with ethical committee, authorities, sponsor etc.), the patient identification log, the signed informed consent forms, and the main study documents (protocol, amendments) for the same time period. The original patient records have to be archived according to the standard procedures of the respective institution, but at least for 10 years.

## **11.0 TRANSLATIONAL RESEARCH**

### **11.1 Immune status in the peripheral blood**

The effect of pembrolizumab on the immune phenotype of the peripheral blood has only marginally been studied so far, but is mandatory to deepen the knowledge on systemic and immune modulating effects of combinations of radiation therapy with immune checkpoint blockade. There exist no analyses about the combination of pembrolizumab with radiation therapy. In this trial pembrolizumab will be administered on day 3 of radiotherapy and repeated every third week.

In treatment arm A (with radiotherapy) a blood sample will be analyzed on day 0 before the first fraction of radiation therapy. Thereafter, in both arms we will analyze blood before each of the first four pembrolizumab administrations. In the following time, blood samples will be analyzed prior to the eighth and twelfth pembrolizumab administrations. One further blood sample should be drawn in the Safety Follow-up Visit. This results in an average of 5 up to a maximum of eight blood samples. These closed meshed analyses will shed light on the answer of the immune system to pembrolizumab with and without radiotherapy and may identify early predictive markers for a future treatment response to pembrolizumab.

We will collect non-clotted whole blood as well as clotted blood for the generation of serum. The patient's material will be collected and stored at the Department of Radiation Oncology Erlangen. We have implemented a biobank which allows storing all blood samples (serum, plasma, and RNA) in a quality-controlled manner. All samples will be processed in the laboratory and stored in 2D Matrix coded tubes. The samples will be managed with sample storage software [LIMS] which allows adding an audit trail to every sample. This enables highest quality of sample storage and the spreading of the samples to all partners for further analyses. The technical equipment for the biobank system (ultra-cold fridges with temperature monitored 24/7, 2D plate barcode-scanner, centrifuges, LIMS software) is fully provided by the Department of Radiation Oncology Erlangen.

In the non-clotted whole blood, a detailed immunophenotyping of all patients will be performed at the Department of Radiation Oncology in Erlangen. The laboratory of Radiation Immunobiology (Prof. Dr. Gaipf) has developed a set of highly modular multicolor flow cytometry protocols to analyze at least 40 different cell subsets including all major immune cells in peripheral blood<sup>47</sup>. These protocols have a special focus on the detection of the expression of activation markers on distinguished immune cells. These analyses can be performed on about 5 ml non-clotted whole blood.

Further, RNA of the immune cells will be extracted and stored for following analysis. Focus will be set on immunological activation markers, cytokine production and pathways of the immunological synapse.

## Protocol/Amendment No.: 717

Blood of the patients will be analyzed on the amount of pembrolizumab-induced antibody dependent cellular cytotoxicity (ADCC) by analyzing common danger signals correlating with ADCC. In particular messengers correlating with immunogenic cell death (HMGB1, HSP70, IL-34) or onset of ADCC (LDH, IFN- $\gamma$ , MCP-1, TNF- $\alpha$ ) will be studied.

## 11.2 PD-L1 in combination with tumor-infiltrating lymphocytes

The immunosuppressive potential of a cancer is of great interest. PD-L1 is a major player in the immunosuppression of inflammatory cells, however there are several other potential immunosuppressive cells like regulatory T cells and M2 macrophages. Another question is whether the inflammatory cells like cytotoxic cells (CD8, M1 macrophages) or antigen presenting cells (dendritic cells, B cells) are functional or immunosuppressed. We have developed a multiparameter and multislice assay to analyze the immunosuppressive potential of the inflammatory cells and the functional activity of the antigen presenting and cytotoxic cells. We use serial sections of the tumor tissue sections and stain it mostly by double stainings shown in table 13. The overall set of slides is scanned by a whole slide scanner. By the use of an image analysis software each image is as accurately as possible aligned to each other. The tumor epithelium and stromal areas are identified and the inflammatory cells and tumor cells are marked by the software. The positions of the tumor and stromal mass and the coordinates of the inflammatory cells are transferred to a database. Now from these data sets the distribution pattern and the distance from each cell to the next cell can be calculated. The calculated cell to cell distances can be compared to simulated distances showing whether cells are randomly distributed and therefore not functional or have shorter distances than the simulated distances and are assessed to be functional due to their interactions with other inflammatory or tumor cells<sup>48-50</sup>. Additionally it is possible to calculate an immunosuppressive score or cytotoxicity score or other multiparameter scores.

Table 13: Multislice staining strategy

	Marker 1	Marker 2	Identified characteristics by marker 1	Identified characteristics by marker 2
1	H3K9me3		Premature senescence	
2	CleavedCaspase3	Ki67	Apoptosis	Proliferation
3	E-Cadherin	HE	Cell-in-cell, budding	Cancer cells
4	CD68	CD163	M1 macrophages (cytotoxic)	M2 macrophages (immunosuppressive)
5	FoxP3	CD8	Regulatory T cells	Cytotoxic T cells
6	PD-L1		Programmed death-ligand 1	
7	CD1a	CD20	Dendritic cells	B cells
8	CD45RO	CD4	Memory T cells	T helper cells
9	PD1		Programmed cell death protein 1	

## **12.0 REFERENCES**

1. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *The New England journal of medicine* 2008;359:1116-27.
2. Knoedler M, Dietz A, C. GT, et al. Cetuximab, fluorouracil (5-FU), cisplatin, and docetaxel as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): Interim results of a randomized phase II clinical trial (CeFCiD). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31:suppl; abstr e17021.
3. Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2015;26:1941-7.
4. Kushwaha VS, Gupta S, Husain N, et al. Gefitinib, Methotrexate and Methotrexate plus 5-Fluorouracil as palliative treatment in recurrent head and neck squamous cell carcinoma. *Cancer biology & therapy* 2015;16:346-51.
5. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009;27:1864-71.
6. Jimeno A, Bauman JE, Weissman C, et al. A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. *Oral oncology* 2015;51:383-8.
7. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *The New England journal of medicine* 2015;372:2018-28.
8. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *The Lancet Oncology* 2015;16:908-18.
9. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *The New England journal of medicine* 2015;372:2521-32.
10. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540-50.
11. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *The New England journal of medicine* 2016;374:2542-52.
12. Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *The Lancet Oncology* 2016;17:717-26.
13. Seiwert T, Haddad R, Gupta S, et al. Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): Preliminary results from KEYNOTE-012 expansion cohort. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015;33:suppl; abstr LBA6008.
14. Ferris RL, Blumenschein G, Fayette J, et al. Further evaluations of nivolumab (nivo) versus investigator's choice (IC) chemotherapy for recurrent or metastatic (R/M) squamous cell carcinoma

**Protocol/Amendment No.: 717**

of the head and neck (SCCHN): CheckMate 141. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34:suppl; abstr 6009.

15. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England journal of medicine 2015;373:23-34.
16. Barker HE, Paget JT, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nature reviews Cancer 2015;15:409-25.
17. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. International journal of radiation oncology, biology, physics 2004;58:862-70.
18. Derer A, Frey B, Fietkau R, Gaipl US. Immune-modulating properties of ionizing radiation: rationale for the treatment of cancer by combination radiotherapy and immune checkpoint inhibitors. Cancer immunology, immunotherapy : CII 2015.
19. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer immunology research 2013;1:365-72.
20. Hiniker SM, Chen DS, Reddy S, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. Translational oncology 2012;5:404-7.
21. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. The New England journal of medicine 2012;366:925-31.
22. Grimaldi AM, Simeone E, Giannarelli D, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunology 2014;3:e28780.
23. Schoenfeld JD, Mahadevan A, Floyd SR, et al. Ipilimumab and cranial radiation in metastatic melanoma patients: a case series and review. Journal for immunotherapy of cancer 2015;3:50.
24. Golden EB, Chhabra A, Chachoua A, et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. The Lancet Oncology 2015;16:795-803.
25. Carbognin L, Pilotto S, Milella M, et al. Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1): Sensitivity Analysis of Trials in Melanoma, Lung and Genitourinary Cancers. PloS one 2015;10:e0130142.
26. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer research 2014;74:5458-68.
27. Lim SH, Hong M, Ahn S, et al. Changes in tumour expression of programmed death-ligand 1 after neoadjuvant concurrent chemoradiotherapy in patients with squamous oesophageal cancer. European journal of cancer 2015;52:1-9.
28. Hecht M, Buttner-Herold M, Erlenbach-Wunsch K, et al. PD-L1 is upregulated by radiochemotherapy in rectal adenocarcinoma patients and associated with a favourable prognosis. European journal of cancer 2016;65:52-60.
29. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. The Journal of clinical investigation 2014;124:687-95.
30. Zeng J, See AP, Phallen J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. International journal of radiation oncology, biology, physics 2013;86:343-9.

**Protocol/Amendment No.: 717**

31. Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2009;15:5379-88.
32. Chandra RA, Wilhite TJ, Balboni TA, et al. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. *Oncoimmunology* 2015;4:e1046028.
33. Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic Radiosurgery for Melanoma Brain Metastases in Patients Receiving Ipilimumab: Safety Profile and Efficacy of Combined Treatment. *International journal of radiation oncology, biology, physics* 2015.
34. Powell SF, Gitau MM, Sumey CJ, et al. Safety of pembrolizumab with chemoradiation (CRT) in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). *J Clin Oncol* 35 (2017) suppl: 6011.
35. Sejpal SV, Bhate A, Small W. Palliative radiation therapy in the management of brain metastases, spinal cord compression, and bone metastases. *Seminars in interventional radiology* 2007;24:363-74.
36. Scorsetti M, Comito T, Tozzi A, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. *Journal of cancer research and clinical oncology* 2015;141:543-53.
37. Siva S, Kirby K, Caine H, et al. Comparison of Single-fraction and Multi-fraction Stereotactic Radiotherapy for Patients with 18F-fluorodeoxyglucose Positron Emission Tomography-staged Pulmonary Oligometastases. *Clinical oncology* 2015;27:353-61.
38. Casamassima F, Livi L, Masciullo S, et al. Stereotactic radiotherapy for adrenal gland metastases: university of Florence experience. *International journal of radiation oncology, biology, physics* 2012;82:919-23.
39. Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *International journal of radiation oncology, biology, physics* 2012;83:878-86.
40. Ricardi U, Badellino S, Filippi AR. Clinical applications of stereotactic radiation therapy for oligometastatic cancer patients: a disease-oriented approach. *J Radiat Res* 2016.
41. Wannemacher M, Debus J, Wenz F. *Strahlentherapie*, 2nd edition. Berlin: Springer-Verlag; 2013.
42. Hristow B, Steven HL, P. CJ. *Radiation Oncology - A question-based review*, 2<sup>nd</sup> edition: Lippincott Williams&Wilki; 2014.
43. Rivelli TG, Mak MP, Martins RE, da Costa e Silva VT, de Castro G, Jr. Cisplatin based chemoradiation late toxicities in head and neck squamous cell carcinoma patients. *Discov Med* 2015;20:57-66.
44. Gray R, Manola J, Saxman S, et al. Phase II clinical trial design: methods in translational research from the Genitourinary Committee at the Eastern Cooperative Oncology Group. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2006;12:1966-9.
45. Korn EL, Arbuck SG, Pluda JM, Simon R, Kaplan RS, Christian MC. Clinical trial designs for cytostatic agents: are new approaches needed? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2001;19:265-72.

**Protocol/Amendment No.: 717**

46. Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:7199-206.
47. Ruhle PF, Fietkau R, Gaipl US, Frey B. Development of a Modular Assay for Detailed Immunophenotyping of Peripheral Human Whole Blood Samples by Multicolor Flow Cytometry. Int J Mol Sci 2016;17.
48. Feichtenbeiner A, Haas M, Buttner M, Grabenbauer GG, Fietkau R, Distel LV. Critical role of spatial interaction between CD8(+) and Foxp3(+) cells in human gastric cancer: the distance matters. Cancer immunology, immunotherapy : CII 2014;63:111-9.
49. Nagl S, Haas M, Lahmer G, et al. Cell-to-cell distances between tumor-infiltrating inflammatory cells have the potential to distinguish functionally active from suppressed inflammatory cells. Oncoimmunology 2016;5:e1127494.
50. Posselt R, Erlenbach-Wunsch K, Haas M, et al. Spatial distribution of FoxP3+ and CD8+ tumour infiltrating T cells reflects their functional activity. Oncotarget 2016.

**13.0 ABBREVIATIONS**

3D-RT	Three-dimensional radiotherapy
5-FU	5-fluorouracil
AE	Adverse Event
ADCC	Antibody dependent cellular cytotoxicity
ADL	Activities of Daily Living
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette–Guérin
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CPS	Combined positive score
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CRT	Chemoradiation
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
CTV	Clinical Target Volume
CUP	Cancer of unknown primary
DEGRO	Deutsche Gesellschaft für Radioonkologie e.V.
DKA	Diabetic ketoacidosis
DSMC	Data Safety Monitoring Committee
DVH	Dose volume histogram
ECI	Event of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency

## Protocol/Amendment No.: 717

EORTC	European Organization for Research and Treatment of Cancer
ERC	Ethics 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 Filtration Rate
GTV	Gross Tumor Volume
hBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
Hr(s)	Hour(s)
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	$\gamma$ Interferon gamma
Ig	Immunglobuline
IGRT	Image guided radiotherapy
IL	Interleukin
IMRT	intensity-modulated radiotherapy
INR	International Normalized Ratio
IRB	Institutional Review Board
iRECIST	RECIST for immune-based therapeutics
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITV	Internal target volume
ISF	Investigator Site File
IV/i.v.	Intravenous
Kg	Kilogram
LA	HNSCC Locally Advanced Head and Neck Squamous Cell Carcinoma
mAb	Monoclonal Antibody
mcL	Microliters
Mg	Milligram

## Protocol/Amendment No.: 717

Mg/kg	Milligram per Kilogram
ml	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum Tolerated Dose
NA	or N/A Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease / Pharmacodynamics
PD-1	Programmed Cell Death Receptor 1
PD-L1	Programmed Cell Death Receptor Ligand 1
PD-L2	Programmed Cell Death Receptor Ligand 2
PFS	Progression Free Survival
PK	Pharmacokinetic
PO	Oral Administration
PR	Partial Response
PTV	Planning Target Volume
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RTOG	Radiation Therapy Oncology Group
QW	Every Week
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RT	Radiotherapy or Radiation Therapy
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SJS	Stevens-Johnson syndrome

**Protocol/Amendment No.: 717**

SmPC	Summary of medicinal Product Characteristics
SRT	stereotactic radiotherapy
t <sub>1/2</sub>	Terminal half-life
TB	Bacillus Tuberculosis
TEN	toxic epidermal necrolysis
TIL	tumor-infiltrating lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VMAT	volumetric modulated arc therapy
WBC	White Blood Cell

## 14.0 APPENDICES

### 14.1 ECOG Performance Status

Table 14: ECOG

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.	

### 14.2 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>)

### 14.3 Response Evaluation Criteria iRECIST

Response evaluation will be performed according to iRECIST\* and RECIST\*\*. These iRECIST criteria are the RECIST 1.1 criteria adapted for immunotherapy.

\* As published in Lancet Oncology:

Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger

**Protocol/Amendment No.: 717**

M, Caramella C, de Vries EG; RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152.

**\*\* As published in the European Journal of Cancer:**

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: 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.

**Product:** Pembrolizumab



94

**Protocol/Amendment No.:** 717

## 15.0 SIGNATURES

### 15.1 Sponsor's Representative

TYPED NAME	MARKUS F. NEURATH
TITLE	Prof. Dr. Sponsor Dean of the Medical Faculty of the Friedrich-Alexander University Erlangen-Nürnberg
SIGNATURE	
DATE SIGNED	28.3.2023

TYPED NAME	RAINER FIETKAU
TITLE	Prof. Dr. Principal Investigator
SIGNATURE	
DATE SIGNED	28.03.23

## Protocol/Amendment No.: 717

**15.2 Investigator**

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any SAEs as defined in the section in the protocol. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	