AIO-Studien-gGmbH

0316-ASG / NEOMUN

NCT03197467

Neoadjuvant anti PD-1 immunotherapy in resectable non-small cell lung cancer

Short title:	NEOMUN
Sponsor:	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin, Germany
Coordinating Investigator (LKP)	Priv.-Doz. Dr. med. Martin E. Eichhorn [redacted] 69126 Heidelberg, Germany
EudraCT Nr.:	2017-000105-20
Protocol identification number:	0316-ASG
Protocol version:	Version 5.0 (22-SEP-2020)

Confidentiality

The contents of the protocol are confidential and may neither be communicated verbally nor in writing without the agreement of the study sponsor.

Contact Addresses

Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin [redacted] E-mail: info@aio-studien-ggmbh.de
Coordinating Investigator (for Germany: LKP)	Priv.-Doz. Dr. med. Martin E. Eichhorn [redacted]
Drug Supply	MSD
Protocol Committee	[redacted]

Approval of the Protocol

[redacted]

24. 09 2020

Date (DD Month YYYY)

[redacted]

SEP / 2020

D Month YYYY)

Investigator's Agreement

I have read the attached protocol entitled

"Neoadjuvant anti PD-1 immunotherapy in resectable non-small cell lung cancer [NEOMUN]"

Version 5.0, 22-SEP-2020

and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice all applicable national regulations as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

I consent to report every serious clinical adverse event as well as any other adverse event as specified in the safety section of this protocol to the safety desk within 24 hours after awareness, whether it is related to study medication or not.

[redacted]

22/SEP/2020

Date (DD Month YYYY)

Synopsis

Protocol No.	0316-ASG
Protocol Version	Final 5.0
Title	***Neoadjuvant anti PD-1 immunotherapy in resectable non-small cell lung cancer [NEOMUN]***
EudraCT No.	2017-000105-20
National Coordinating Investigator	Priv.-Doz. Dr. med. Martin E. Eichhorn Thoraxklinik – Universität Heidelberg Roentgenstrasse 1 69126 Heidelberg [redacted]
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin [redacted]
Study design	The study is designed as an open-label, single arm, prospective, monocenter, phase II study of pembrolizumab in a neoadjuvant setting in patients with non-small cell lung cancer of Stage II/IIIA suitable for curative intent surgery
Indication	Resectable NSCLC stage II/IIIA
Proposed countries / Total number of sites	Germany Number of sites total: 1
Primary objective	To assess feasibility and safety of a neoadjuvant application of pembrolizumab To assess antitumor activity of pembrolizumab with regard to clinical and pathologic tumor response
Secondary objectives	To assess the impact of neoadjuvant pembrolizumab on patient disease free and overall survival.
Exploratory objectives	To explore potential predictive biomarkers for pembrolizumab efficacy Immune cell imaging: • immune cell infiltrates in and around the resected tumor • tumor tissue- and serum cytokine profiles • Hypothesis generation on potential biomarkers predicting efficacy of pembrolizumab using multi-OMICS analysis
Planned sample size	N=30.

Inclusion criteria	1. Cooperation and willingness to complete all aspects of the study 2. Signed and dated written informed consent must be given prior to study inclusion 3. Histological or cytological confirmed NSCLC. 4. Clinical stage II-IIIA according to the TNM classification, 7th edition. stage IIIa: T1/T2 N2 ($IIIa_{1-3}$ Robinson classification) 5. Adequate disease staging by PET/CT performed and resectability established. 6. At least 1 measurable lesion according to RECIST 1.1 7. Age ≥ 18 years 8. ECOG performance status 0 - 1 9. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in in the protocol, for the course of the study through 120 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. 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. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. 10. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in protocol, 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. 11. Adequate bone marrow function, liver and renal function: a. Absolute neutrophil count ≥ 1.5 x 10^9/L b. Thrombocytes ≥ 100 x 10^9/L c. Hemoglobin ≥ 9 g/dL without transfusion or EPO dependency (within 7 days of assessment)

	d. INR < 1.4 and PTT < 40 seconds during the last 7 days before therapy e. Bilirubin < 1.5 x upperlimit of normal f. AST (GOT) and ALT (GPT) < 2.5 x ULN g. Albumin ≥ 2.5 mg/dL h. Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl): ≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN 12. adequate lung and cardiac function for intended lung resection according to German S3 guideline
Exclusion criteria	1. Anticancer treatment during the last 30 days prior to start of treatment, including systemic therapy, radiotherapy or major surgery 2. Participation in a clinical trial within the last 30 days prior to study treatment 3. History of allogeneic tissue/solid organ transplant 4. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. 5. Evidence of interstitial lung disease. 6. cT4 tumor 7. Symptomatic acute cardiovascular or cerebrovascular disease 8. Known active HBV, HCV or HIV infection 9. Has any other active infection requiring systemic therapy. 10. Patients with active tuberculosis 11. Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-Programmed cell death-ligand 1 (anti-PD-L1), anti-PD-L2, anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

	12. A diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. 13. Patient has had a prior monoclonal antibody within 4 weeks prior to study Day 1 14. Patient 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., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. [Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study. If subject received major surgery, he/she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.] 15. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study. 16. Has received a live vaccine within 30 days prior to the first dose of trial treatment. [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.] 17. Has known hypersensitivity to pembrolizumab or any of constituents of the product. 18. Other active malignancy requiring treatment Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

	19. Lactating or pregnant women, women of child-bearing potential who do not agree to the usage of highly effective contraception methods (allowed methods of contraception, meaning methods with a rate of failure of less than 1% per year are implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner). Women of childbearing potential must have a negative pregnancy test (serum β-hCG) at Screening. 20. Any psychiatric illness that would affect the patient's ability to understand the demands of the clinical trial 21. Patient has already been recruited in this trial 22. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 23. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
Investigational drug	Pembrolizumab at fixed dose
Treatment phase	Pembrolizumab 200 mg q3w i.v. for 2 cycles After completion of immunotherapy lobectomy/bilobectomy with curative intent is scheduled.
Study rationale	Survival prognosis in non-small cell lung cancer is strongly disease stage dependent. Patients diagnosed with clinical stage IA have a 5-year survival rate of 82% compared to 6% in patients with stage IV disease [1]. Surgery with curative intent is the standard treatment approach in stage I and II patients and a subgroup of stage III patients. Despite radical tumor resection this treatment approach still is associated with a considerable risk of disease relapse in particular in stage II and IIIA disease. The overall 5-year relapse rate following curative intent surgery is 52% [2]. Standard adjuvant therapy was shown to postpone tumor recurrence by 4-5 month. However, total rate of tumor relapse was not suppressed by

	adjuvant therapy. Meta-analysis of clinical trial data indicates that adjuvant chemotherapy or radio-chemotherapy significantly increase overall survival. However, the effect is small and accounts for a 4% improvement in the 5-year overall survival rate. Neoadjuvant chemotherapy is an alternative standard treatment approach and typically consists of 3 cycles of platinum-based combination chemotherapy. Comparable to the adjuvant setting a neoadjuvant approach confers a 5% increase in the 5-year survival rate [3]. In terms of efficacy no difference between a pre- or postoperative chemotherapy approach can be determined [4]. In the light of the efficacy results it is clear, that improved multimodal treatment strategies are direly needed in order to improve long term survival following curative intent surgery. Immunotherapies made a large impact in the treatment of advanced stages of malignant diseases leading to marketing approvals for several tumor entities including NSCLC. Neoadjuvant immunotherapy by application of anti-PD-1 targeting antibodies is a logical conclusion based on the treatment reality described above. Clinical data on neoadjuvant treatment is scarce but encouraging and several trials investigating anti-PD-1/PD-L1 checkpoint inhibition (e.g. nivolumab, durvalumab, atezolizumab) are ongoing. Consequently, the scope of this trial will be the generation of pilot data on efficacy, safety and feasibility of neoadjuvant anti-PD-1 immunotherapy by pembrolizumab. The research endeavor will be flanked by a translational research program to elucidate potential predictive biomarkers and to investigate the mode of action of anti PD-1 treatment in NSCLC patients.
Rationale for sample size and tests to be used	A phase II approach will be used to generate preliminary hypothesis generating data. No formal sample size estimation has been performed. The scope is to gather information on feasibility, safety and efficacy. Target sample size is N=30.

	The rationale for the sample size of this trial is based on ethical, clinical as well as scientific considerations. The neo-adjuvant treatment approach with an immune check-point inhibitor is highly experimental with only limited data on safety and feasibility available. Therefore, only a small number of patients should be subjected to this experimental treatment. Nevertheless, the sample size should allow the generation of statistically meaningful evidence for feasibility and safety to permit the decision to further develop this treatment approach. With a sample size of N=30 and assuming that the number of events follows a binomial distribution B(30,p), events with an incidence rate p > 9.5% will be observed at least once with a 95% probability. This observation limit will exclude individual pembrolizumab related SAEs but covers most of the historical reference events/rates of the primary endpoints in this trial as well as the early stopping rule. The degree of the potential evidence provided by a sample size of N=30 is summarized in the statistics section of the protocol.

Endpoints / Statistical analysis	The trial design will be a phase II trial, with descriptive outcome assessments of:
	Primary endpoints:
	• frequency and severity of adverse events including peri- and post-operative complications (grade 2-4 AEs according to NCI-CTCAE V4.03)
	  ○ number of patients treated in compliance with protocol
	• Tumor response evaluation
	  Clinical response parameters:
	  ○ response rates (Δ tumor size / lymph node size), according to RECIST 1.1 criteria
	  ○ Δ PET-activity (standardized uptake value [SUV])
	  Pathologic response parameters:
	  ○ Pathologic regression grading according to Junker criteria

	Secondary endpoints: • disease free survival • overall survival	
Study plan	FPI LPI LPO EoS (after 24 month FU of LPO)	Q2/2018 after approx. 36 month (Q2/2021) after approx. 40 month (Q4/2021) after approx. 64 month (Q4/2023)

Schedule of Study Assessments

Study Phase / Procedure	Screening	Treatment phase		Pre-Surgery	Dis-charge	End of treatment	Follow-up
Visit	**SCR**	**V1**	**V2**	**PS**	**D**	**EOT**	**FU1 – FUx**
Time windows	**Day - 28 to 0**	**Day 1**	**Day 21 +/- 3 days**	**Day 43-50**	**Day 60-74**	**6 wks. after surgery**	**every 3 months**
Informed consent	X						
Demographics (age, gender, race)	X						
Tumor diagnosis	X						
Cancer history	X						
Medical history (incl. smoking status)	X						
Previous treatments	X						
Tumor assessments (PET)-CT, RECIST 1.1	X			X			
Tumor staging (PET-CT, MRI brain)	X						
Chest X-ray	X		X	X	X	X	
Cardiac evaluation (12-lead ECG)	X		(X)[1]	X		X	
Physical examination[2]	X		X	X	X	X	
Body weight and height / BSA[3]	X		X	X		X	
Vital signs (BP, HR, body temperature)	X	(X)[8]	X	X	X	X	
Lung function test blood gas values	X		X	X		X	
ECOG status	X		X	X		X	
Pregnancy test (if applicable)	X	(X)[8]					
Hematology[4]	X	(X)[8]	X	X	X	X	
Coagulation	X	(X)[8]	X	X	X	X	
Clinical chemistry[5]	X	(X)[8]	X	X	X	X	
tumor marker	X			X		X	
TSH[6]	X		X	X	X	X	
In- / Exclusion criteria	X						
Biomarkers (blood sample)		X	X	X	X	X	
Tumor tissue[9]	X				X		
HR-QoL	X			X		X	
Treatment (V1/V2)		Pembrolizumab 200 mg i.v	Pembrolizumab 200 mg i.v. .				

Study Phase / Procedure	Screening	Treatment phase		Pre-Surgery	Dis-charge	End of treatment	Follow-up
Visit	**SCR**	**V1**	**V2**	**PS**	**D**	**EOT**	**FU1 – FUx**
Time windows	**Day - 28 to 0**	**Day 1**	**Day 21 +/- 3 days**	**Day 43-50**	**Day 60-74**	**6 wks. after surgery**	**every 3 months**
Concomitant medication	X	Continuously					
Concomitant procedures	X	Continuously					
Adverse events	X	Continuously					X[7]
Subsequent cancer therapy							X
Survival status							X

[1] if clinically indicated. Consult a specialist if clinically abnormal and exclude any immune-related myocarditis.

[2] Full examination is required at baseline and end of treatment. Focused clinical examination shall prevail throughout the course of treatment.

[3] Body height will only be measured at screening.

[4] Full blood count including blood differential test will be performed at baseline, after start of treatment (V2) and further indicated time points throughout treatment and at end of study.

[5] Sodium, potassium, calcium, magnesium, phosphate, AST, ALT, PTT/INR, LDH, total bilirubin, creatinine, creatinine clearance, albumin, tumor marker CEA, Cyfra 21-1

[6] To be done at baseline and 3 weeks after start of treatment (V2) and further indicated time points throughout treatment and at end of study. If rising TSH is detected, a full assessment of fT3 and fT4 shall be performed and signs of hormone depletion shall be monitored clinically.

[7] Follow-up of ongoing SAEs until resolution or stabilization. Serious adverse events are recorded until 90 days after last dose of IMP or for 6 weeks after surgery if the subject initiated new anticancer therapy (e.g. radiochemotherapy). Pregnancies occurring in a study subject are recorded from time of signed informed consent until 120 days after last dose of IMP.

[8] Repeat assessment if SCR assessment is older than 7 days.

[9] Post-op. tumor regression grading.

Safety reporting contact information (SAE / Pregnancy)

In the case of a serious adverse event (SAE) or pregnancy safety desk must be contacted within 24 hours.

Contact details for safety reporting are provided in the Investigator Site File.

The safety desk will inform MSD Germany Pharmacovigilance (Email: [redacted]) and other appropriate persons about all SAEs, as well as pregnancy and events of clinical interest, within 1 working day of knowledge of the event.

Glossary of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AIO	Arbeitsgemeinschaft Internistische Onkologie
ALT (SGPT)	Alanine aminotransferase
AMG	Arzneimittelgesetz (German Drug Law)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
BSA	Body Surface Area
CI	Confidence interval
CR	Complete response
CRF / eCRF	Case report form / electronic Case report form
CSR	Clinical study report
CT	Computed tomography
CTC	Common terminology criteria
CTCAE	Common terminology criteria of adverse events
D	Day
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e.g.	For example
EMA	European Medicines Agency
EOT	End of treatment
etc	Et cetera
FPFV	First patient first visit
FU	Follow up
g	Gram
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung
HR	Heart rate
HR	Hazard ratio
IADL	Instrumental Activities of Daily Living
IB	Investigators' Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
i.e.	That is
IMP	Investigational medicinal product
ITT	Intent to treat
i.v. / IV	Intravenous
kg	kilogram
L	Liter
LKP	Leiter der klinischen Prüfung (Co-ordinating Investigator)
LPFV	Last patient first visit
LPLV	Last patient last visit
m²	Square meter (body surface area)
mAb	Monoclonal Antibody

mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCT	National Center for Tumor Diseases
NOAEL	no observed adverse effect level
OP	Operation
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death receptor 1
PD-L1	Programmed death receptor ligand 1
PFS	Progression free survival
PP	Per Protocol
PR	Partial response
q3w	Every 3 weeks
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RICTOR	Rapamycin-insensitive companion of mTOR
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SCR	Screening
SD	Stable disease
SOC	Standard of Care
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardized uptake value
TBD	To be determined
TTFS	Time to Failure of Strategy
TPS	Tumor Proportion Score
V	Version
WHO	World Health Organization

Table of Contents

1 Background and Rationale

1.1 Disease Background

In Germany lung cancer is the most frequent form of cancer death in male and the third most frequent malignant disease in women [5]. A steady trend to increasing incidence numbers in the female population is observed and the most important risk factor for disease remains tobacco smoking. Lung cancer diagnosis is associated with a poor prognosis and 5-year survival rates are 16% in male and 21% in female patients [5]. Non-small cell lung cancer (NSCLC) is the dominant form comprising 85-90% of all lung cancers. NSCLCs are divided into three main subgroups; squamous cell carcinoma, large cell carcinoma and adenocarcinomas, the latter of which is generally the most frequent (60-70% of NSCLC). Curative intent surgery represents the primary treatment modality in approximately 30% of NSCLC patients. However, even in patient cohorts of specialized high volume lung cancer centers more than 50% of patients develop tumor recurrence within 5 years following curative intend surgery. (see Figure 1).

1.2 Pembrolizumab

1.2.1 Pembrolizumab Background

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® (pembrolizumab) has recently been approved in the United Stated and the E.U. for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Additionally, pembrolizumab has received marketing approval for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumors express PD-L1 and who have received at least one prior chemotherapy regimen.

On 05-Aug-2016 the US FDA approved KEYTRUDA®, at a fixed dose of 200 mg Q3W, for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing

chemotherapy. Under the FDA's accelerated approval regulations, this indication for KEYTRUDA® is approved based on tumor response rate and durability of response. For HNSCC patients, PD-L1 testing is not needed prior to use of KEYTRUDA®. The FDA-approved dose of KEYTRUDA® is 200 mg Q3W.

1.2.2 Mechanism of Action

The PD-L1 and PD-L2 can be found on tumor cells and this receptor-ligand interaction is one of the major pathways used by the cancerous cells to suppress the body's immune response to the tumor, as binding of either PD-L1 or PD-L2 to PD-1 inhibits T cell activation triggered through the T cell receptor.
Evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and a favorable prognosis in various malignancies. Correspondingly, a high expression of PD-L1 (and to a lesser extent PD-L2) on tumor cells has been found to correlate with a poor prognosis and survival rate in various types of cancer. Pembrolizumab can prevent the binding of PD-L1 and PD-L2 to the PD-1 receptor thus preventing its tumor suppressing effects on the immune response. Therefore, it is predicted that Pembrolizumab has the potential to improve the prognosis and survival rates of patients with various malignancies. For this reason Pembrolizumab is being developed to treat patients with various malignancies.

1.2.3 Pembrolizumab Non Clinical Data

1.1.1.1 Pharmacology

Pembrolizumab binds to human and Cynomolgus monkey PD-1 with comparable affinity and blocks the binding of human and Cynomolgus monkey PD-1 to PD-L1 and PD-L2 with comparable potency. Pembrolizumab does not cross-react with dog, rat, or mouse PD-1. Pembrolizumab does not bind immunoglobulin (Ig) superfamily members cluster of differentiation 28 (CD28), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or inducible T-cell costimulator (ICOS).

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer subjects, and nonhuman primates. In T-cell activation assays using human donor blood cells, the half-maximal effective concentration has been approximately 0.1 to 0.3 nanomolar (nM). In addition to

interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNɣ), and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. In the in vitro peripheral blood mononuclear cell (PBMC) and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low and comparable to those induced by trastuzumab. Pembrolizumab does not induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Using anti–murine PD-1 surrogate antibodies, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti–PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU), and combination therapy results in increased complete tumor regression rates in vivo. Studies also revealed that immunosuppressive doses of dexamethasone included in combination with agents used in standard-of-care treatment for NSCLC do not reduce the anti-tumor efficacy of an anti–murine PD-1 surrogate antibody.

1.1.1.2 Toxicology and Toxicokinetics

Refer to the current Investigator's Brochure of pembrolizumab for preclinical data.

1.2.4 Pembrolizumab Clinical Safety and Efficacy

Pharmacokinetics

PK data are presented in the IB from a total of 1818 PK-evaluable subjects with advanced melanoma (KN001 [Parts B and D], KN002), NSCLC (KN001 Parts C and F), advanced solid tumors (including triple negative breast cancer [TNBC], head and neck squamous cell carcinoma [HNSCC], urothelial carcinoma, gastric cancer [KN012]), and hematological cancers (KN013 and KN023). The observed PK profile of pembrolizumab was typical when compared with other immunoglobulin G (IgG) mAbs with a $t_{1/2}$ of approximately 3 weeks [6].

Safety

To date, Pembrolizumab has been generally well tolerated, as expected based on preclinical findings and work conducted with other anti-PD-1 monoclonal antibodies. No serious infusions reactions have been reported and less than 1% of patients assayed so far have tested positive for the presence of Pembrolizumab antibodies (anti-drug antibodies - ADA). Where Pembrolizumab antibodies have been detected its presence does not appear to have impacted on overall levels of patient exposure.

The majority of subjects (97.4%) in pembrolizumab monotherapy trials experienced one or more AEs, 73.7% experienced one or more AEs reported as drug-related by the investigator. The percentage of subjects who experienced SAEs was lower; 37.2% of subjects experienced one or more SAEs; and 11.9% of subjects discontinued due to an AE. 10.0% of subjects experienced a drug-related SAE, as determined by the investigator.

The 5 most frequently reported AEs were: fatigue (37.3%), nausea (24.5%), decreased appetite (22.5%), diarrhea (22.3%), and cough (22%). The 5 most frequently reported SAEs were pneumonia (3.0%), pleural effusion (1.7%), pneumonitis (1.6%), dyspnea (1.6%) and pulmonary embolism (1.5%).

The 5 most frequently reported adverse events considered drug-related by the investigator were fatigue (24.2%), pruritus (16.7%), rash (13.8%), diarrhea (12.3%), and nausea (10.9%). The 5 most frequently reported serious adverse events considered drug related by the investigator were pneumonitis (1.6%), colitis (0.9%), diarrhea (0.6%), pyrexia (0.4%) and autoimmune hepatitis (0.3%).

Full details on pembrolizumab safety can be found in the current Investigator’s Brochure [6].

Efficacy

3 important clinical studies were conducted to evaluate the efficacy of pembrolizumab in the treatment of NSCLC: KN001, and KN010 and KN024.

KN001 was an open-label, Phase 1, first-in-human study conducted to evaluate clinical activity of pembrolizumab as a single agent in 2 cancers, including NSCLC. There were several dosing regimens (see IB). Part C and Part F of KN001 enrolled subjects with NSCLC.

KN010 was a randomized, adaptively designed Phase 2/3 trial of pembrolizumab at 2 dose levels vs docetaxel in subjects with NSCLC with PD-L1 positive tumors who had experienced disease progression after platinum-containing systemic therapy. Subjects were randomized according to their tumor proportion score (TPS) (extent of PD-L1 expression) defined as follows: a TPS ≥ 50% was considered strongly positive and a TPS°= 1% to 49% was considered weakly positive.

In KN001 the independently confirmed objective response rate according to RECIST 1.1 was 41% among all treated subjects (N=61) with strong PD-L1 expression in the tumor [6].

For the KN010 Intent-to-treat (ITT) Population (TPS≥50%), median OS was 14.9 months in the 2 mg/kg Q3W pembrolizumab arm and 17.3 months in the 10 mg/kg Q3W pembrolizumab arm compared with 8.2 months in the docetaxel arm. In the TPS≥50% stratum, an HR of 0.54 (p=0.00024, median 14.9 months) was observed for OS comparing pembrolizumab 2 mg/kg Q3W to docetaxel [6].

For the KN010 ITT population with TPS≥1% (total population), the OS HR for pembrolizumab 2 mg/kg vs docetaxel was 0.71 (95% CI: 0.58, 0.88) with a p-value of 0.00076. The OS HR for pembrolizumab 10 mg/kg vs docetaxel was 0.61 (95% CI: 0.49, 0.75) with a p-value <0.00001.

For the KN010 ITT Population (TPS≥50%), median PFS was 5.2 months in the 2 mg/kg Q3W and 10 mg/kg Q3W arms compared with 4.1 months in the docetaxel arm. The HR for PFS was 0.58 (p=0.00009, median 5.2 months) observed for PFS comparing pembrolizumab 2 mg/kg Q3W to docetaxel, and an HR of 0.59 (p=0.00007, median 5.2 months) was observed for PFS comparing pembrolizumab 10 mg/kg Q3W to docetaxel. For the KN010 ITT population with TPS≥1% (total population) PFS results did not meet the predefined criteria for statistical significance.

Among patients in KN010 with a tumor proportion score of 50% or greater, responses occurred in 30% of patients in the pembrolizumab 2 mg/kg group, 29% of patients in the pembrolizumab 10 mg/kg group, and 8 % of patients in the docetaxel group ($p<0.0001$ for each pembrolizumab group *vs* docetaxel). In the total population, 62 (18%) of 344 patients versus 64 (18%) of 346 patients versus 32 (9%) of 343 had responses ($p=0.0005$ for 2 mg/kg *vs* docetaxel and $p=0.0002$ for 10 mg/kg *vs* docetaxel). All responses were partial responses. Median time to response was 9 weeks in each treatment group [7].

Recently the KEYNOTE-024 trial investigating the use of pembrolizumab, in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1, met its primary endpoint. In this trial, pembrolizumab was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the secondary endpoint of overall survival (OS). Based on these results, an independent Data Monitoring Committee (DMC) has recommended that the trial be stopped, and that patients receiving chemotherapy in KEYNOTE-024 be offered the opportunity to receive pembrolizumab.

Conclusion:

Overall, the results from KN001 and KN010 demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in subjects with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. The PD-L1 selection employed in KN010 identified patients more likely to benefit from pembrolizumab and resulted in favorable HRs in OS compared to docetaxel.

1.3 Study Rationale

Survival prognosis in non-small cell lung cancer is strongly disease stage dependent. Patients diagnosed with clinical stage IA have a 5-year survival rate of 82% compared to 6% in patients with stage IV disease [1]. Surgery with curative intent is the standard treatment approach in stage I and II patients and a subgroup of stage III patients. Despite radical tumor resection this treatment approach still is associated with a considerable risk of disease relapse in particular in stage II and IIIA disease. The overall 5-year relapse rate following curative intent surgery is 52% [2]. Standard adjuvant therapy was shown to postpone tumor recurrence by 4-5 month. However, total rate of tumor relapse was not suppressed by adjuvant therapy. Meta-analysis of clinical trial data indicates that adjuvant chemotherapy or radio-chemotherapy significantly increase overall survival. However, the effect is small and accounts for a 4% improvement in the 5-year overall survival rate. Neoadjuvant chemotherapy is an alternative standard treatment approach and typically consists of 3 cycles of platinum-based combination chemotherapy. Comparable to the adjuvant setting a neoadjuvant approach confers a 5% increase in the 5-year survival rate [3]. In terms of efficacy no difference between a pre- or postoperative chemotherapy approach can be determined [4].

In the light of the efficacy results it is clear, that improved multimodal treatment strategies are direly needed in order to improve long term survival following curative intent surgery. Immunotherapies made a large impact in the treatment of advanced stages of malignant diseases leading to marketing approvals for several tumor entities including NSCLC. Neoadjuvant immunotherapy by application of anti-PD-1 targeting antibodies is a logical conclusion based on the treatment reality described above. Clinical data on neoadjuvant treatment is scarce but encouraging [8, 9] and trials investigating anti-PD-1/PD-L1 checkpoint inhibition (e.g. nivolumab, durvalumab, atezolizumab) ongoing.

First preliminary data on neoadjuvant anti-PD-1 therapy in NSCLC patients presented on the ESMO conference 2016. In stage I-III NSCLC patients neoadjuvant nivolumab therapy induced pathological tumor response in 80% (12/15) of patients and major pathologic response in 40% (6/15) treated with only 2 cycles of nivolumab administered 2 and 4 weeks prior to tumor resection [8]. The results were confirmed

at final analysis, with a major pathologic response observed in 43% of all treated subjects (95% CI 24-63%; 9/21 subjects) [9].

Consequently, the scope of this trial will be the generation of pilot data on efficacy, safety and feasibility of neoadjuvant anti-PD-1 immunotherapy by pembrolizumab. The research endeavor will be flanked by a translational research program to elucidate potential predictive biomarkers and to investigate the mode of action of anti PD-1 treatment in NSCLC patients.

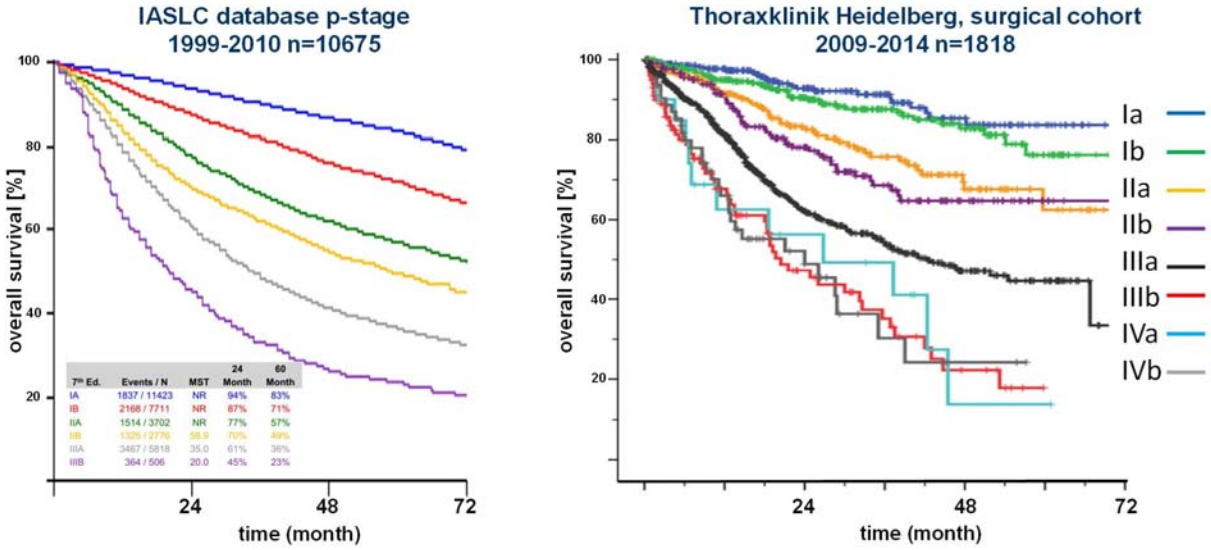

Figure 1- Stage dependent survival in NSCLC. Left panel - The IASLC Lung Cancer Staging Project [1] ; right panel - Thoraxklinik Heidelberg

1.3.1 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB).

Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in

melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Rationale for a 2-cycle treatment regimen

The rationale for a 2-cycle regimen can be derived from the following three aspects:

1. Clinical efficacy: Results from a pilot study with nivolumab in a neoadjuvant setting in stage I-III NSCLC indicate that 2 cycles of anti-PD-1 inhibition result in tumor response and permitted successful tumor resection the majority of patients (see also section 1.3)[9].
2. Patient safety: Shorter treatment courses (i.e. 2 cycles of neoadjuvant treatment vs. 3 cycles or more) are preferable as it would reduce the risk of inoperability due to treatment emergent adverse events (e.g. immune-mediated pneumonitis) or tumor progression.
3. Ethical consideration: Patients with resectable lung cancer have the reasonable expectation to undergo tumor resection as soon as possible. A waiting period of 6 weeks until surgery resulting from the application of 2 doses of neoadjuvant immunotherapy still represents a clear and acceptable perspective for the patient for tumor removal.

1.4 Risk-Benefit Analysis

The neoadjuvant treatment approach is an accepted and frequently applied treatment strategy in stage II-III lung cancer. The general risk of this strategy is a delay of the surgical intervention which may render the tumor unresectable after the completion of the pharmaceutical intervention. This potential risk similarly applies to this trial. As a measure of risk reduction the extent of the neoadjuvant treatment with pembrolizumab will be limited to 2 cycles (i.e. 6 weeks) which corresponds to the typical duration of classical chemotherapy regimens and is considered safe. Additional risks arise from the insufficient knowledge of the perioperative safety of an immunotherapy such as

pembrolizumab. Typically, in pivotal studies extensive temporal safety margins between immunotherapies and surgical interventions have been mandated. It will be the goal of this pilot study targeting a small patient cohort to generate additional safety data in this context. The safety profile of anti-PD-1/PD-L1 antibodies is generally favorable compared to classical platinum-combination protocols and no particular adverse events (e.g. wound healing disorders) are known which would preclude a use of pembrolizumab in the neoadjuvant setting. Additionally, comprehensive AE treatment guidelines and dose modification recommendations have been established and incorporated in this protocol.

Pembrolizumab is approved in stage IV NSCLC with a PD-L1 tumor proportion score ≥50%. However, the predictive role of PD-L1 expression in early stage NSCLC is unclear. Pilot data from nivolumab in a neoadjuvant setting in NSCLC did not show a correlation between tumor response and resectability and PD-L1 positivity [9]. Furthermore, comparative studies between NSCLC biopsies and surgically resected specimens revealed major discordance with regard to PD-L1 positivity [10, 11]. Given the uncertainty of the temporal and spatial dynamics of PD-L1 expression in early stage NSCLC it does not seem justified to exclude patients based on PD-L1 expression status. Therefore, an all-comers population will be addressed.

Neoadjuvant immunotherapy may convey a number of benefits: Immunotherapeutics/checkpoint-inhibitors have demonstrated significant improvements in tumor size reduction, which potentially results in increased operability. Reduced toxicities and the simplicity of the treatment protocol may similarly increase operability due to increased compliance and efficacy. A neoadjuvant approach may be more advantageous compared to an adjuvant treatment since it is speculated that an intact blood supply of the tumor is a prerequisite for an efficient immune-surveillance and enhances immune-cell-tumor cell interaction and ultimately tumor cell killing. Furthermore, immunotherapeutics such as pembrolizumab are hypothesized to exert anti-tumor activity through the eradication or prevention of micro-metastasis, resulting in extended disease free intervals and increased overall survival. In summary, we consider the risk-benefit ratio to favor the conduct of this trial. As additional safety measure, an independent data monitoring committee will review patient safety at a planned interim analysis after 15 study subjects have been treated

with preoperative intent and will give recommendations with regard to trial continuation or early termination.

2 Objectives of the Study

2.1 Primary Objective

- To assess feasibility and safety of a neoadjuvant application of pembrolizumab.
- To assess antitumor activity of pembrolizumab with regard to clinical and pathologic tumor response

2.2 Secondary Objectives

To assess the impact of neoadjuvant pembrolizumab on patient disease free and overall survival.

2.3 Exploratory Objectives

To explore potential predictive biomarkers for Pembrolizumab efficacy by immune cell and cytokine analysis:

- Inflammatory infiltrates in and around the resected tumor
- tumor tissue and serum cytokine profiles
- Hypothesis generation on potential biomarkers predicting efficacy of pembrolizumab using multi-OMICS analysis

2.4 Primary endpoint

- frequency and severity of adverse events including peri- and post-operative complications (grade 2-4 AEs according to NCI-CTCAE V4.03)
    - number of patients treated in compliance with protocol
- tumor response evaluation

  clinical response parameters:
    - response rates (Δ tumor size / lymph node size), according to RECIST 1.1 criteria
    - Δ PET-activity (standardized uptake value [SUV])

  Pathologic response parameters:
    - Pathologic regression grading according to Junker criteria [12]

2.5 Secondary endpoints

- disease free survival
- overall survival

2.6 Exploratory endpoints:

- prognostic value of tumor shrinkage
- prognostic value of inflammatory infiltrates in and around the resected tumor
- serum- and tumor tissue cytokine concentrations
- multi-OMICS tissue analysis approach for markers and mechanisms

3 Overview of Study Design and Dosing Regimen

The study is designed as an open-label, single arm, prospective, monocentric, phase II study of pembrolizumab in a neoadjuvant setting in patients with non-small cell lung cancer of Stage II/IIIA suitable for surgery.

During the treatment phase, patients will receive intravenous pembrolizumab 200 mg q3wks. for 2 cycles or occurrence of non-tolerable toxicity. After completion of immunotherapy lobectomy or bilobectomy with curative intent is scheduled. After end of protocol treatment, patients will be treated individually according to local standards.

3.1 Treatment Phase

After screening, patients will be treated with Pembrolizumab every 3 weeks for 2 cycles. A non-invasive tumor assessment by PET-CT will be performed before neoadjuvant treatment and before curative intent surgery. If tumor progression or non-tolerable toxicity is noted during immunotherapy, an End of Treatment (EOT) visit will be performed and the patient will enter the follow-up phase.

3.1.1 Surgery

Surgery is the standard treatment in the neoadjuvant treatment approach and not a study specific procedure. The procedure of standard lobectomy/bilobectomy with systematic lymph-node dissection is well described in all manuals of thoracic surgery. In brief, patients undergo general anaesthesia and endobronchial double-lumen intubation. Blood pressure, heart rate, electrocardiographic trace, respiratory frequency and oxygen saturation are monitored continuously throughout the operation by an anaesthesiologist. Thoracotomy is usually performed through the fourth or fifth intercostal space. Vascular and bronchial structures at the level of the hilum are prepared and resected along with the corresponding lobe and lymph node containing fatty tissues. A radical systematic lymph node dissection accomplishes a standard lobectomy procedure. Vessels can be closed by ligation, suture or stapler. The bronchus can be closed by suture or stapler. Depending on the anatomical consideration of the interlobar fissure and the different techniques in use, the division can be performed at the beginning or the end of the surgery and can be done by

stapler, cautery or any other technique. Surgical technique for closure of vessels and bronchus, and the different techniques of parenchymal sparing have to be described for each patient in the OP-records. In special cases video-assisted thoracic surgery (minimal-invasive; small incisions) may replace open thoracotomy (larger incision). Two standard chest tubes are placed at the end of the operation. Postoperative patients will be monitored on the intensive care unit for at least 12 hours.

3.2 End of Treatment

End of Treatment is defined as 6 weeks post surgery (approx. 4 weeks post discharge). In patients who discontinue during the treatment phase, an End of Treatment (EOT) visit will be performed within 28 days after treatment discontinuation.

3.3 Follow-up Phase

After treatment discontinuation, follow-up evaluations will be performed every 3 months in order to collect information on relapse, survival status and subsequent cancer treatment until end of study.

3.4 End of Study

All enrolled patients will be followed up until the end of the study. The study will be terminated as soon as the last patient has completed at least 24 months of follow-up.

3.5 Assignment of Patients to Treatment

A total of 30 patients will be enrolled into the study and will receive neoadjuvant treatment of 2 cycles of pembrolizumab.

3.6 Study sites

The study will be conducted in one center only, which will recruit all required patients.

3.7 Study Duration

Study duration is approximately 64 months measured from FPI.

FPI	Q2/2018
LPI	after approx. 36 month
LPO	after approx. 40 month
EoS (after 24 month FU of LPO)	*after approx. 64 month*

4 Selection of the Study Population

4.1 Target Population

Patients with resectable NSCLC stage II/IIIA eligible for immunotherapy and surgery.

4.2 Inclusion Criteria

1. Cooperation and willingness to complete all aspects of the study
2. Signed and dated written informed consent must be given prior to study inclusion
3. Histological or cytological confirmed NSCLC
4. Clinical stage II-IIIA according to the TNM classification, 7th edition:
   stage IIIa: T1/T2 N2 ($IIIa_{1-3}$ Robinson classification)
5. Adequate disease staging by PET/CT and brain MRI
6. At least 1 measurable lesion according to RECIST 1.1
7. Age ≥ 18 years
8. ECOG performance status 0 - 1
9. Female subjects of childbearing potential (Section 7.6.6) must be willing to use an adequate method of contraception as outlined in Section 7.6.6 – Contraception and Pregnancy, for the course of the study through 120 days after the last dose of study medication.
   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
   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. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Male subjects of childbearing potential (Section 7.6.6) must agree to use an adequate method of contraception as outlined in Section 7.6.6 – Contraception and Pregnancy, 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.

11. Adequate bone marrow function, liver and renal function:
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L
    b. Thrombocytes ≥ 100 x 10^9/L
    c. Hemoglobin ≥ 9 g/dL without transfusion or EPO dependency (within 7 days of assessment)
    d. INR < 1.4 ULN and PTT < 40 seconds during the last 7 days before therapy
    e. Bilirubin < 1.5 x upper limit of normal
    f. AST (GOT) and ALT (GPT) < 2.5 x ULN
    g. Albumin ≥2.5 mg/dL
    h. Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl):

       ≤1.5 X upper limit of normal (ULN) **OR**

       ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
12. Adequate lung and cardiac function for intended lung resection according to German S3 guideline

4.3 Exclusion Criteria

1. Anticancer treatment during the last 30 days prior to start of treatment, including systemic therapy, radiotherapy or major surgery
2. Participation in a clinical trial within the last 30 days prior to study treatment
3. History of allogeneic tissue/solid organ transplant
4. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
5. Evidence of interstitial lung disease.
6. cT4 tumor
7. Symptomatic acute cardiovascular or cerebrovascular disease
8. Known active HBV, HCV or HIV infection
9. Has any other active infection requiring systemic therapy.
10. Patients with active tuberculosis

11. Prior therapy with an anti-Programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-Programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)
12. A diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
13. Patient has had a prior monoclonal antibody within 4 weeks prior to study Day 1
14. Patient has had prior chemotherapy, targeted small molecule therapy, or radiation therapy in history.
15. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. *Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.*
16. Has received a live vaccine within 30 days prior to the first dose of trial treatment. [*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.*]
17. Has known hypersensitivity to pembrolizumab or any of the constituents of the product.
18. Other active malignancy requiring treatment

    Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
19. Lactating or pregnant women, women of child-bearing potential who do not agree to the usage of highly effective contraception methods (allowed

methods of contraception, meaning methods with a rate of failure of less than 1% per year are implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner). Women of childbearing potential must have a negative pregnancy test (serum β-hCG) at Screening.

20. Any psychiatric illness that would affect the patient's ability to understand the demands of the clinical trial
21. Patient has already been recruited in this trial
22. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
23. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

5 Schedule of Assessment and Procedures

Please refer to the Schedule of Assessments for an overview.

Data will be collected via an electronic Case Report Form (eCRF) for each eligible patient. The investigator should confirm eligibility of the patient according to the inclusion and exclusion criteria of the study. All patients will provide written Informed Consent before any study specific assessment is performed. A study specific assessment is defined as a procedure that is not part of the routine assessments performed for diagnostic purposes or standard care. Screening assessments should occur within 28 days of the first administration of study drug.

Patients not meeting the inclusion/exclusion criteria will not be enrolled into the study. Patients should receive their first dose of study treatment as soon as possible after they have been intended to be treated with study medication.

5.1 Study Assessments

5.1.1 Tumor assessments

All tumor evaluation is performed according to RECIST (Response Evaluation Criteria In Solid Tumors, V. 1.1, 2009, see Appendix 2 – RECIST 1.1 and table below) using CT scan or MRI scan. The baseline tumor assessment must be recorded and measured within 28 days prior to treatment start. The imaging technique for baseline tumor measurement(s) may be either computed tomography (CT, including spiral CT) or MRI according to investigator's choice and local routine standard of care. However, the same imaging technique must be used for all consecutive tumor assessments of the same patient. Whenever possible the same personnel should perform the tumor image evaluation.

All lesions identified at screening have to be assessed at each scheduled tumor measurement. Patients with measurable lesions will be eligible for inclusion. Measurable lesions must have at least one diameter of 20 mm with conventional techniques and at least 10 mm with spiral CT scan. Where there are several lesions, assessment is based on the sum of the longest diameters of the individual target lesions. Lymph nodes with a short axis of ≥ 15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the

sum of lesions in calculation of tumor response. Nodes that shrink to < 10 mm short axis are considered normal. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions.

In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled tumor assessment should be performed.

Response Criteria

Definitions of the criteria used to determine objective tumor response/ Evaluation of target lesions:

Complete response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters on study (this includes the baseline sum if that is the smallest on study).
Progressive disease	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. In the absence to clinical deterioration, a validation scan shall be performed after 4 weeks. Treatment continuation is warranted if tumor growth ≤20% of SLD. If PD is confirmed, the date of the pervious scan is counted as time point for PD. **or** Appearance of one or more new lesion. Note that the appearance of a single new lesion also requires validation of progression by another scan after 4 weeks.

5.1.2 Other Clinical Assessments

5.1.2.1 ECOG Performance Status

To be eligible for study entry, patients must have an ECOG performance score of 0 to 1. The patients' ECOG performance status will be assessed at the screening visit, during treatment every 3 weeks, before surgery, and at the EOT-visit.

5.1.2.2 Medical history

Medical history including cancer and treatment history will be reviewed and recorded at screening visit (≤ 1 year before enrolment).

5.1.2.3 ECG

A 12-lead ECG will be performed at screening, pre-surgery and at EOT and during the treatment phase if clinically indicated.

5.1.2.4 Chest X-ray

Routine chest X-ray according to local standard will be performed at screening, during neoadjuvant treatment Q3W, pre- and post-surgery and at EoT.

5.1.2.5 Quality of life

Quality of life will be assessed by the EORTC QLQ-C30 questionnaire.
QoL will be assessed at screening, before surgery and at EoT.

5.1.2.6 Lung function/blood gas analysis

Lung function test in order to evaluate the operability of a patient should be done prior to or at screening. Availability of an adequate lung function test is an inclusion criterion and the test should not be older than 4 weeks at screening. The tests include body plethysmography, assessment of diffusion capacity and blood gas analysis. Lung function tests should be repeated during pembrolizumab treatment Q3W, prior to surgery and at EoT.
Parameters to be assessed are: FEV1, VC, FEV/VC, TLCO, PaO_2, $PaCO_2$, SaO_2, pH.

5.1.2.7 Physical examination

A full physical examination will be performed at the screening visit and at EOT. During treatment a focused clinical examination at every cycle as well as pre-surgery and at discharge is sufficient.

5.1.2.8 Vital signs

Vital signs (blood pressure, heart rate, body temperature) as well as body weight will be measured at the screening visit, at each visit during treatment phase, before surgery, at dis-charge and at the EoT-visit. Body height will be measured at screening only.

5.1.2.9 Translational Research

Additional blood and tumor samples will be collected in patients as described in the translational research plan which is deposited in the ISF.

5.1.3 Safety Assessments

See section 7

5.1.4 Laboratory Assessments

Blood samples will be taken for hematological and serum chemistry monitoring at screening and every 3 weeks +/- 3 days during treatment phase, before surgery and at EOT. The local laboratory will perform the analyses and provide reference ranges.

5.2 Study Procedures

5.2.1 Screening Procedures (day -28 to 0)

NOTE: Any routine procedure which is performed during the screening window may be used as a screening assessment in this trial. Documentation of any screening procedure in the eCRF can only be performed after informed consent of the patient. All patients will be screened and screening procedures performed within 28 days prior to start of study treatment include the following:

Signed Informed Consent	Obtained prior to any study specific assessment

Demographics and medical history	○ Age, gender, race ○ Tumor diagnosis ○ Previous and concurrent relevant diseases ○ Previous treatments ○ Tobacco consumption in pack years
Tumor measurement according to RECIST 1.1 (CT or MRI)	See section 5.1.1
Tumor assessments • CT or MRI	Whole body PET-CT and MRI brain scans (or CT brain if MRI is not feasible) are required.
Cardiac evaluation	12-lead ECG
Physical examination and vital signs	○ Physical examination ○ Body height, weight ○ Vital signs measurements will include body temperature, pulse and blood pressure
ECOG performance status	See Appendix 1 – ECOG Performance Status
Serum pregnancy test	A serum pregnancy test will be performed in pre-menopausal women and women who are menopausal for < 2 years. In case the sampling date for serum pregnancy testing exceeds 7 days before treatment start, a urine test is required for confirmation of the absence of pregnancy.
Lung function	Body plethysmography / blood gas analysis, diffusion capacity
Hematology	Hemoglobin, erythrocytes, platelets, leukocytes, absolute neutrophils (ANC), basophils, eosinophils, lymphocytes, monocytes
Clinical chemistry	Sodium, potassium, calcium, magnesium, albumin phosphate, AST, ALT, PTT/INR, LDH, total bilirubin, creatinine, creatinine clearance (see section 18.4 Appendix 4), TSH
tumor marker	CEA, Cyfra 21-1

5.2.2 Treatment Phase

For V1 no particular assessments are required. However, the following assessments need to be repeated if the Screening assessment is older than 7 days measured from first dose of IMP: Hematology, pregnancy test, clinical chemistry, coagulation, vital signs. ConMed and AE documentation may need to be updated if required.

During treatment phase the following assessments and procedures will be performed for V2 unless a different time point is mentioned specifically:

Cardiac evaluation	12-lead ECG, transthoracic echocardiogram (TTE) if clinically indicated
Physical examinations and vital signs	• Physical examination • Body weight, BSA • Vital signs measurements will include body temperature, pulse and blood pressure
ECOG performance status	Day 1 of each immunotherapy cycle, see Appendix 1 – ECOG Performance Status
Pregnancy test	During treatment phase the pregnancy test should be repeated if the investigator considers it necessary. A serum or urine pregnancy test will be performed in pre-menopausal women and women who are menopausal for < 2 years.
Hematology	Hemoglobin, erythrocytes, platelets, leukocytes, absolute neutrophils (ANC), basophils, eosinophils, lymphocytes, monocytes
Clinical chemistry + coagulation	Sodium, potassium, calcium, magnesium, phosphate, AST, ALT, PTT/INR, LDH, total bilirubin, creatinine, creatinine clearance (see section 18.4 Appendix 4)TSH. If rising TSH is detected, a full assessment of fT3 and fT4 shall be performed and signs of hormone depletion shall be monitored clinically.
Concomitant medication,	Assessed on an ongoing basis

Adverse events	

5.2.3 Pre-surgical visit

Tumor measurement according to RECIST 1.1 (CT or MRI)	See section 5.1.1
Tumor assessments • CT or MRI	Whole body PET-CT
Cardiac evaluation	12-lead ECG
Physical examination and vital signs	○ Physical examination ○ weight ○ Vital signs measurements will include body temperature, pulse and blood pressure
ECOG performance status	See Appendix 1 – ECOG Performance Status
Serum pregnancy test	A serum pregnancy test will be performed in pre-menopausal women and women who are menopausal for < 2 years if clinically indicated.
Lung function	Body plethymography / blood gas values
Hematology	Hemoglobin, erythrocytes, platelets, leukocytes, absolute neutrophils (ANC), basophils, eosinophils, lymphocytes, monocytes
Clinical chemistry + coagulation	Sodium, potassium, calcium, magnesium, phosphate, AST, ALT, PTT/INR, LDH, total bilirubin, albumin, creatinine, creatinine clearance (see section 18.4 Appendix 4), TSH
Concomitant medication, Adverse events	Assessed on an ongoing basis

5.2.4 Discharge visit

Hematology	Hemoglobin, erythrocytes, platelets, leukocytes, absolute neutrophils (ANC), basophils, eosinophils, lymphocytes, monocytes
Clinical chemistry + coagulation	Sodium, potassium, calcium, magnesium, phosphate, AST, ALT, PTT/INR, LDH, total bilirubin, creatinine, creatinine clearance (see section 18.4 Appendix 4), TSH
Concomitant medication, Adverse events	Assessed on an ongoing basis + peri-operative complications
Post-op. tumor tissue analysis	Regression grading accord. to Junker criteria (see section 18.3 Appendix 3)

5.2.5 End of Treatment Visit

Cardiac evaluation	12-lead ECG
Physical examination and vital signs	○ Physical examination ○ weight ○ Vital signs measurements will include body temperature, pulse and blood pressure
ECOG performance status	See Appendix 1 – ECOG Performance Status
Lung function	Body plethymography / blood gas values
Hematology	Hemoglobin, erythrocytes, platelets, leukocytes, absolute neutrophils (ANC), basophils, eosinophils, lymphocytes, monocytes
Clinical chemistry + coagulation	Sodium, potassium, calcium, magnesium, phosphate, AST, ALT, PTT/INR, LDH, total bilirubin, albumin, creatinine, creatinine clearance (see section 18.4 Appendix 4), TSH
Concomitant medication, Adverse events	Including peri-operative complications

5.2.6 Follow-up

After discontinuation of treatment, all patients will be followed-up for survival every 3 months. First visit of the follow-up period will take place 3 months after EOT visit. Follow-up of the individual patient will continue until death or until study is terminated. The following information will be collected during the follow-up:

- Survival data
- Subsequent anti-cancer therapy
- Study drug related adverse events continuing from treatment phase will be followed-up until the event has resolved or stabilized

5.2.7 End of Study

The final statistical analysis will be performed when the last patient has completed at least 24 months of follow-up or death occurred, whichever comes first.

5.2.8 Planned Treatment of the Patient after End of Treatment Phase

After completion of study at the End-of-Treatment-Visit, patients will generally be treated at the discretion of the investigator according to medical routine.

5.3 Removal of Patients from Treatment

Patients will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/removed if necessary, to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Patients that will be withdrawn from the study will not be replaced.

Patients will be removed from further treatment for the following reasons:

- Disease progression
- Continued unacceptable toxicities despite optimal treatment or dose reduction
- During the treatment a delay of study treatment of more than 6 weeks
- Delay from screening to start of study treatment of more than 31 days
- Intercurrent illness, at the investigator’s discretion
- Withdrawal of consent

- Non-compliance / Lost to follow-up
- Pregnancy
- Termination of the study by the sponsor

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT and the Follow-up visits should be performed, if possible. In any case, the eCRF section entitled “End of Treatment” must be completed.

Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the eCRF.

If a patient withdraws consent for further study treatment, the patient should still be followed for progression and survival. If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

5.4 Study discontinuation

The whole study will be stopped at the discretion of the sponsor (with or without IDMC recommendation) in the event of any of the following:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AE with a negative impact on the risk/benefit assessment
- Negative benefit/risk assessment due to new information
- Further external scientific evidence that this regimen might result in a suboptimal risk-benefit-assessment for the whole group of patients or for a distinct subgroup
- medically unacceptable risks for the treatment of the patients
- At the interim analysis, if the rate of unresectability is equal or greater 20%; i.e. if 3/15 or more study subjects did not undergo surgery as planned according to the protocol (unresectable or excessive delay of surgery). [early stopping rule]

6 Investigational Product

6.1 Investigational Medicinal Product (IMP)

An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

The IMP in this study is Pembrolizumab. It will be delivered to the participating center free of charge. Details on the distribution will be described in a specific operation procedure with appropriate forms attached. All other concomitant medical treatment will be prescribed by the treating physician, as this prescription is within the framework of standard of care.

The relevant information on the drug characteristics, storage, application, mode of action and adverse reactions is included in the respective and current Investigator's Brochure and pharmacy manual provided in the ISF.

The investigator will ensure that the study medication is used only in accordance with the protocol.

6.1.1 Supply of pembrolizumab

Pembrolizumab will be supplied by MSD and will bear a label with the identification required by local law, the protocol number, drug identification and dosage as well as the statement "For Clinical Trial Use Only". The packaging and labeling of the study medication will be in accordance with MSD standards and local regulations. All the requirements of Annex 13 of the Good Manufacturing Practices guideline for labeling investigational drug will be fulfilled.

Upon arrival of study medication the local pharmacy will check the IMP for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the Sponsor upon discovery.

The study medication must be stored according to the details on the product label. The drug label indicates the storage temperature. The relevant information on the drug characteristics, storage, application, mode of action and adverse reactions is included in the respective and current Investigator's Brochure of pembrolizumab.

The investigator will ensure that the study medication is used only in accordance with the protocol.

6.1.2 Documentation

The responsible pharmacist will maintain records of the inventory at the site, the use for each patient and delivery, storage and destruction. The investigator will also maintain records that adequately document that patients were provided the doses specified in the protocol and the responsible pharmacist will reconcile all study medication received from the central pharmacy.

The date, time and amount will be documented in the eCRF by the investigator.

6.2 Preparation and Administration of Pembrolizumab

6.2.1 Drug Name, Formulation and Storage

Drug name: pembrolizumab (MK-3475) CAS number 1374853-91-4

Dosage: 100 mg/vial

Formulation:

- Pembrolizumab Solution for Infusion is provided in Type I glass vials intended for single use only.
- Pembrolizumab Solution for Infusion 100 mg/vial is a liquid DP (manufactured using the fully formulated DS with L-histidine as buffering agent, polysorbate 80 as surfactant, and sucrose as stabilizer/tonicity modifier).

Reconstitution: The liquid drug product can be further diluted with normal saline or 5%dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered.

Appearance: clear to opalescent solutions, essentially free of visible particles.

Labelling: Labelling of study drug will be in accordance with German GCP-V § 5 and other applicable national regulations in the German Drug Law (AMG) and GCP-V in effect.

Storage:

- Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion.
- In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C for up to 18 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- From a microbiological point of view Pembrolizumab (MK-3475) has to be used immediately once the vial has been opened. If not used immediately, the responsibility for storage time and storage conditions lie within the handler.

6.2.2 Route of Administration

Pembrolizumab is administered as an i.v. infusion with 200 mg fixed dose corresponding to 2 vials (100 mg/ vial). The treatment interval is q3w (Day 1 of each 21 day cycle). Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

The following infusion set materials are compatible with Pembrolizumab (MK-3475):

- PVC Infusion set that is plasticized using DEHP
- PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
- Polyethylene lined PVC infusion set
- PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
- Polyurethane set

*Contact Sponsor for materials not listed above

- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any

adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be as mentioned above).

- Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.
- Infuse Pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.
- In case of infusion reactions, infusion rate may differ:
    - Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes
    - Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. However, when it is necessary to infuse a larger volume (i.e., 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.
- Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered according to institutional guidelines for saline flushing.

6.2.3 Infusion reactions – Course of action and premedication

Infusion reactions – although rare – may occur during the administration of Pembrolizumab. Patients experiencing infusion reaction need to be treated appropriately as detailed in Table 2.

In case of grade 2 infusion reactions patients may be prophylactically pre-medicated upon subsequent study drug applications. Detailed guidelines for handling of infusion reactions are provided in Table 2.

6.2.4 Compliance

The Investigator or a pharmacist or other appropriate individual, who is designated by the local Principal Investigator, should maintain records of the inventory at the site, the use for each patient and delivery, storage and destruction. Investigators should

maintain records that adequately document that patients were provided the doses specified in the protocol and reconcile all investigational product(s) received from the sponsor.

The investigator should ensure that the investigational product(s) are used only in accordance with the protocol.

The investigational product(s) should be stored as specified by the Sponsor and in accordance with applicable regulatory requirements.

6.3 Dose Modifications

6.3.1 Dose Modification and Discontinuation of pembrolizumab for adverse reactions

Dose modifications in terms of dose reductions are not allowed in this study. Dose modifications in terms of pausing of treatment or discontinuation may be required due to AEs.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 1 below. See Section 6.3.2 for supportive care guidelines, including use of corticosteroids.

Table 1: Dose Modification Guidelines for Drug-Related Adverse Events: *For more details please see 6.3.2 'supportive measure guidelines'.*

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4		Resume pembrolizumab when patients are clinically and metabolically stable

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Treatment Discontinuation
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c] (e.g. skin related AEs, such as toxic epidermal necrolysis)	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

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

[2b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated for the next scheduled dose; Refer to

– Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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 after not more than 6 weeks after the last dose, unless otherwise discussed with the

Sponsor. The reason for interruption should be documented in the patient's study record.

6.3.2 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

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

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 2 - Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6.4 Concomitant Medication and Treatment

Patients may continue their baseline medication(s) according to the recommendations of the responsible physician. All concomitant medication(s) must be reported in the eCRF. Any therapeutic, or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s) and any clinical findings. Patients should receive full supportive care including transfusion of blood and products, antibiotics, etc. where applicable. The treatment details have to be recorded in the eCRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 21 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 21 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs).

Additionally, any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded.

Supportive care for treatment-related symptoms will be offered as needed to all patients in this study.

Prohibited Medications

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

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) 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
- Radiation therapy

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

7 Assessment of Safety

It is the responsibility of the investigators to report all adverse events in the case report form. Any serious adverse event (SAE) must be reported within 24 hours to the safety desk who will forward the SAEs to the Coordinating Investigator, sponsor and MSD within one working day.

Contact details for safety reporting are provided in the Investigator Site File.

7.1 Reference safety documents

The current version of the Investigator's Brochure of Pembrolizumab will be used as reference document and will be provided to the investigators in the Investigator's File.

7.2 Adverse Events definitions

7.2.1 Adverse Events

An adverse event (AE) is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." (ICH E6: section 1.2).

An adverse event 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 (investigational) product, whether or not considered related to the medicinal (investigational) product.

7.2.2 Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence (adverse event) that at any dose:

- results in death,

- is life-threatening (subject was at immediate risk of death at the time of the event),
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly / birth defect or,
- any other significant medical condition.

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious i.e. important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require interventions to prevent one of the other outcomes listed above (e.g. emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical condition” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Hospitalization for performing of protocol-required procedures or administration of study treatment or hospitalizations for procedures planned prior to study start and elective hospitalizations are not classified as an SAE.

Progression of the underlying malignant disease and symptoms caused by progression of the underlying tumor disease need not to be reported as SAE in this protocol, unless progression or symptoms of progression are assessed as causally related to study medication.

7.2.3 AEs of Special Interest (Events of Clinical Interest)

Events of clinical interest for this trial are:

1. **an overdose of pembrolizumab, as defined in Section 7.2.6, 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.

7.2.4 Other reportable events

Other reportable events of this trial are:

- a new cancer (that is not a condition of the study);
- an AE associated with an overdose.

7.2.5 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current version of the Investigator's Brochure of Pembrolizumab. Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the reference safety document would be considered "unexpected".
A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety document. All suspected adverse reactions related to the IMP which occur in the concerned trial and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

7.2.6 Overdose

For subjects treated with pembrolizumab an overdose will be defined as any dose of 1,000 mg or greater (exceeding 5x the protocol prescribed dose).

7.3 Assessment of relationship - Adverse drug reaction

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

In case of a missing causality assessment in the eCRF or SAE reporting form, the event will be regarded as "probably related" unless further specified.

A serious ADR (SADR) is an adverse drug reaction that meets the definition of a serious event (provided below).

7.4 Assessment of severity

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

If an adverse event occurs which is not contained in the CTCAE version 4.03, the five-point scale below will be used.

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

7.5 Safety recording and reporting requirements

7.5.1 Recording periods

- Adverse events are recorded from time of signed informed consent until 6 weeks (EoT visit) after surgery.
- Serious adverse events are recorded from time of signed informed consent until 90 days after last dose of IMP or for 6 weeks after surgery if the subject initiated new anticancer therapy (e.g. radio-chemotherapy)
- Pregnancies occurring in a study subject are recorded from time of signed informed consent until 120 days after last dose of IMP.

7.5.2 Recording and Reporting requirements

Adverse events in general: All adverse events are documented by the participating site in the patient's medical records and the eCRF. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by patients are properly captured in the patient's medical records (source data).

The following adverse event attributes must be assigned by the investigator:

- adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known),
- event description (with detail appropriate to the event),
- dates of onset and resolution,
- seriousness (yes / no),
- severity (according to NCI CTCAE V4.03),
- assessment of relatedness to study treatment (see section 7.3),
- outcome:
    - recovered / resolved
    - recovered / resolved with sequelae

  - not recovered / not resolved
  - deteriorating/worsening
  - fatal
  - unknown (only applicable if patient is lost to follow-up); and
- action taken:
  - none
  - dose reduced (new dose)
  - study drug temporarily interrupted
  - study drug permanently discontinued (stop date)
  - not applicable
  - unknown

Serious adverse events:

- For each patient any adverse event or abnormal laboratory test value that is serious occurring during the course of the study must be reported immediately (within 24 hours / GCP-V § 12(4)) after awareness to the safety desk (contact details are provided in the Investigator Site File) utilizing a completed SAE Report Form.

- Serious Adverse Events that are unexpected and considered related to IMP and occur after the completion of the trial should be reported to the sponsor (AIO-Studien-gGmbH) within one working day [ICH E2A III.E.3].

Events of clinical interest: Selected non-serious and serious adverse events that are also known as Events of Clinical Interest (ECI) are subject to expedited reporting by the investigator.

- For the time period beginning when the consent form is signed (registration) until start of treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours of investigators awareness to the safety desk 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 start of treatment through 6 weeks following surgery, any ECI, or follow up to an ECI, whether or not related to IMPs, must be reported within 24 hours of investigators awareness to safety desk.

Other reportable events: For each patient any 'other reportable' event occurring until 6 weeks after surgery must be reported immediately (within 24 hours) after investigator's awareness to the safety desk.

Pregnancy: Pregnancies occurring during study treatment and up to 120 days after last dose must be reported by the investigator on the **Pregnancy Report Form** within 24 hours after awareness to the safety desk.
Follow up case reports have to be provided as new information becomes available.
If an SAE is experienced in addition to or related to the pregnancy e.g. an induced or spontaneous abortion, also an SAE Report has to be sent to the safety desk within 24 hours / GCP-V § 12(4) after first knowledge.

Overdose: If an adverse event(s) is associated with ("results from") the overdose of IMP, the adverse event(s) is reported as a **serious adverse event**, even if no other seriousness criteria are met. An SAE Report has to be sent to the safety desk within 24 hours of investigators awareness.

If an overdose is administered 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." An SAE Report has to be sent to the safety desk within 24 hours of investigators awareness.

Abnormal Laboratory results: Abnormal laboratory test results will be recorded on the laboratory results pages of the eCRF. Laboratory-test-value abnormalities should additionally be considered an AE in case they are:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

In general it is the investigator's responsibility to review all abnormal laboratory results and to determine if a given value represents a clinically significant change compared to previously obtained values and results in an Adverse Event or not.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the eCRF.

7.5.3 Sponsor obligations

The Sponsor will ensure compliance with all regulatory reporting requirements including the notification of the appropriate Ethics Committees, Competent Authority of all serious adverse events occurring at the site in accordance with national law, ICH Good Clinical Practice and European / EMA requirements.

A Sponsor representative will medically review all SAE reports.

A Sponsor representative will forward SAE, ECI and pregnancy reports within one working day to MSD.

Every SAE, being assessed by either the investigator or the sponsor as suspected to be related to IMP und assessed as being either unexpected or unexpected with regard to outcome or severity of the event will be reported by the sponsor as SUSAR to the competent authority, responsible ethics committee and investigators of the trial in line with the national regulations in effect (German drug law [AMG] and GCP-V § 13).

Fatal or life-threatening SUSARs must be reported as soon as possible, but no later than 7 days; further important information to these cases may be reported as follow-up within additional 8 days. All others SUSARs have to be reported no later than 15 days.

Also all adverse events which can change the benefit-risk ratio of the study drugs or otherwise fulfill the criteria outlined in GCP-V §13 Abs.4 have to be handled/reported as SUSARs.

7.6 Handling of Safety Parameters

7.6.1 Adverse events

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Medically significant adverse events regardless of causality will be followed until resolved or considered stable. All subjects with serious adverse events must be followed up for outcome.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-treatment assessment and be under medical supervision until symptoms cease or the condition becomes stable.

7.6.2 Overdose of pembrolizumab

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

7.6.3 Treatment and Follow-up of Adverse Events

Adverse events, especially those for which the relationship to test drug is not "unrelated", should be followed up until they have returned to baseline status or stabilized. If a clear explanation is established it should be recorded on the eCRF. All subjects with serious adverse events must be followed up for outcome.

7.6.4 Treatment and Follow-up of Events of Clinical Interest

See section 6.3.2

7.6.5 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and / or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded in the eCRF.

7.6.6 Contraception and Pregnancy

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

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

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

(1) 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

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†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, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

Subjects should be informed that taking the 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 study medication initiation (or 14 days prior to the initiation of study medication 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.

A female patient must be instructed to immediately inform the investigator if she becomes pregnant during the study. The study treatment must immediately be stopped and the patient must be withdrawn from the study. The investigator should counsel the patient; discuss the risks of continuing the pregnancy, and possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

7.6.7 Adverse Drug reactions with Concomitant Medication

The investigators must be aware that for all concomitant medications the regulations of post marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

8 Statistical Methods and Sample Size

8.1 Trial design and hypotheses

The study is designed as an open-label, single arm, prospective, monocentric, phase II study of pembrolizumab in a neoadjuvant setting in patients with non-small cell lung cancer of Stage II/IIIA suitable for curative intent surgery. It is formally hypothesized that pembrolizumab applied in the neoadjuvant setting is feasible and safe and additionally a clinically meaningful pilot data for efficacy can be observed. On a preliminary basis, feasibility will be declared if the rate of successfully performed resections without extended delays is ≥80% (Feasibility criterion).

8.2 Sample Size Calculation

A phase II approach will be used to generate preliminary hypothesis generating data. No formal sample size estimation has been performed. The scope is to gather information on feasibility, safety and efficacy.

Target sample size is N=30

The rationale for the sample size of this trial is based on ethical, clinical as well as scientific considerations. The neo-adjuvant treatment approach with an immune check-point inhibitor is highly experimental with only limited data on safety and feasibility available. Therefore, only a small number of patients should be subjected to this experimental treatment. Nevertheless, the sample size should allow the generation of statistically meaningful evidence for feasibility and safety to permit the decision to further develop this treatment approach.

With a sample size of N=30 and assuming that the number of events follows a binomial distribution B(30,p), events with an incidence rate p > 9.5% will be observed at least once with a 95% probability. This observation limit will exclude individual pembrolizumab related SAEs but covers most of the historical reference events/rates of the primary endpoints in this trial as well as the early stopping rule.

The degree of the potential evidence provided by a sample size of N=30 is summarized in Table 3.

Table 3 -- Reported reference data and exact CI under a sample size of N=30 [Clopper Pearson method] [13-15]

Adverse event / endpoint	Reported Frequency	95% CI for sample size of N=30
AE rate in Pembrolizumab monotherapy trials	97.4%	83.9 – 100.0
Drug related AE rate in Pembrolizumab monotherapy trials *	73.7%	54.5 – 88.0
SAE rate in Pembrolizumab monotherapy trials *	37.2%	20.4 – 56.7
Drug related SAE rate in Pembrolizumab monotherapy trials *	10 %	2.1 – 26.5
Cumulative rate of the 5 most frequent SAEs in Pembrolizumab monotherapy trials and potential impact on neo-adjuvant treatment approach and/or surgery [pneumonia (3.0%), pleural effusion (1.7%), pneumonitis (1.6%), dyspnea (1.6%) and pulmonary embolism (1.5%)] *	9.4%	1.8 – 25.7
number of patients treated in compliance with protocol / Feasibility of resection and early stopping rule #	80 %	61.4 – 92.3
Radiologic response (CR or PR) per RECIST 1.1 §	10 %	2.1 – 26.5
Pathologic response (grade IIb or higher as per Junker criteria) §	43 %	25.2 – 62.3
* See also section 1.2.4 and IB of pembrolizumab # Feasibility criterion § Chaft et al. (J Clin Oncol 35, 2017 suppl; abstr 8508) [9]		

8.3 Evaluation categories of the patients

8.3.1 Intent-to-Treat population

The Intent-to-Treat population (ITT) includes all enrolled.

8.3.2 Per-Protocol population

The Per-Protocol set (PP) will comprise all patients of the Intent-to-Treat population, if the following criteria are additionally met:

- Administration of at least one study treatment.
- All of the major inclusion criteria, none of the major exclusion criteria are fulfilled.
- Documentation of a tumor assessment after start of study treatment.
- Absence of other major protocol violations such as wrong treatment received.

Protocol violations resulting in an exclusion from the Per-Protocol population will be described in the Clinical Study Report.

8.3.3 Safety population

The safety population consists of all patients who received at least one dose of treatment medication.
Patients who cannot be included in any of the above mentioned analysis populations will be excluded from the statistical analyses. Any recorded data of these patients will be listed in the appendix to the Clinical Study Report.

8.4 Methods of Statistical Analysis

8.4.1 General statistical considerations

The statistical evaluation will be carried out by sponsor delegate . Statistical analysis is based on the International Conference on Harmonization (ICH) Guidelines „Structure and Content of Clinical Study Reports“ and “Statistical Principles for Clinical Trials”.

All data recorded in the eCRF describing the sample, the efficacy and the safety will first be analyzed descriptively. Categorical data will be presented in tables with frequencies and percentages.

Continuous data will be summarized with at least the following: frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. Descriptive analyses will be summarized.

Statistical test between changes of parameters over time will be performed for continuous as well as categorical variables. One way repeated measures analysis of

variance, Wilcoxon signed rank test, Fisher`s exact test and other appropriate tests will be used where applicable. Further details will be given in the Statistical Analysis Plan.

Number of patients with protocol deviations during the study and listings describing the deviations will be provided.

For the analysis of Adverse Events, summary tables will be generated for the incidence of AEs overall and by severity. This will also be done for Serious Adverse Events. The AE summary tables will provide the number and percentage of patients with adverse events. All safety analyses will be performed within the safety population.

For laboratory parameters, the distribution over time (mean values) as well as changes from randomization will be computed and reported with descriptive statistics.

The details of the statistical analysis will be defined in a Statistical Analysis Plan, which will be prepared before database closure.

8.4.2 Demographics and baseline characteristics

All demographic and clinical characteristics recorded at baseline will be submitted to descriptive analyses using descriptive statistics by means of listing and tables.

8.4.3 Efficacy evaluation

Primary efficacy parameter:

Efficacy of the neoadjuvant treatment approach will be evaluated by radiologic tumor response (RECIST 1.1 assessment of base line and pre-surgery CT/MRI), by changes of standardized maximal uptake values (SUVs) of the primary tumor quantified by PET-scans, as well as a pathologic regression grading of resected tumor material according to Junker (see Appendix 18.3).

Secondary efficacy parameters:

Time-to-event measures (OS, DFS) will be analyzed by means of Kaplan-Meier curves.

Details on the analysis of secondary parameters will be given in the Statistical Analysis Plan.

8.4.4 Safety evaluation

Adverse events:

All information recorded such as onset date, stop date, duration, maximum intensity, seriousness, relationship to study drug and outcome will be listed.

Summary tables will be presented. These tables provide the number and percentage of patients with adverse events. Associated adverse event tables present the total number of patients reporting at least one specific event and the maximum toxicity grade. Thus, patients reporting more than one episode of the same event are counted only once by the worst grade per patient.

Tabulations consist of the number and percentages of patients involved per CTC category and CTC term, the highest relation to study drug, and the maximum severity. Special tables will be displayed for CTC grade III / IV adverse events and for adverse events resulting in discontinuation of the trial. Additionally, analysis will be restricted to adverse events judged to be at least possibly related to study drug.

Laboratory parameters:

Abnormal laboratory parameters will be tabulated according to incidence and severity according to NCI CTCAE V4.03 and analyzed descriptively.

9 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) has been convened to assess the safety data, and provide recommendations to the Sponsor and Coordinating Investigator upon the stop or continuation of the study. The members of the IDMC serve in their individual capacity and provide their expertise and recommendations. The IDMC will review cumulative study data to evaluate subject safety, conduct an interim analysis and reassess the risk/benefit of the study.

The role and responsibilities of the IDMC are described in detail in a separate IDMC Charter.

10 Data Quality Assurance

The overall procedures for quality assurance of clinical study data are described in the Standard Operation Procedures of either the Sponsor or Sponsor delegate. Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of the drug accountability log by the investigator. Data for this study will be recorded via eCRF by the site from the source documents. Data are reviewed and checked for omissions, apparent errors, and values requiring further clarifications using computerized (automatic) and manual procedures. Data queries requiring clarification are communicated to the site for resolution via the eCRF. Only authorized personnel will make corrections to the clinical database and an audit trail will document all corrections.

11 Ethical Aspects

11.1 Declaration of Helsinki / Good Clinical Practice

The Declaration of Helsinki is the accepted basis for clinical study ethics, and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the protocol.

The trial will be performed in accordance with the Declaration of Helsinki, as decided upon by the 18th World Medical Assembly, Helsinki, Finland, June 1964 (amended by subsequent World Medical Assembly Somerset West, South Africa, October 1996,). The declaration is included as appendix.

Additionally, it is the responsibility of all engaged in research on human beings to ensure that the study is performed in accordance with the international Good Clinical Practice standards and according to all local laws and regulations concerning clinical studies.

11.2 Patient Information and Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of aim, importance, anticipated benefits, and potential hazards and consequences of the study according to applicable local laws. Written informed consent must be obtained before any study specific procedures are performed. It must be also explained to the patient that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason without incurring any penalty or withholding of treatment on the part of the investigator.

With the declaration of consent the patient agrees that data on his disease are recorded within the framework of the clinical trial and that they are transferred to the sponsor in a pseudonymized way.

The subject / patient also agrees to allow the monitor / auditor / health authorities to verify the collected patient data against the subject's / patient's original medical records for the purpose of source data verification.

The informed consent form personally signed and dated by the patient and the investigator and must be kept on file by the investigator(s), and documented in the

eCRF and the subject's medical records. The investigator confirms obtaining the written informed consent to the sponsor.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue in the study.

If the family doctors are informed of their patients' participation in the clinical study, this should be mentioned in the consent form.

11.3 Independent Ethics Committees and Regulatory Authorities

11.3.1 Approval of the study by the Regulatory Authority and Independent Ethics Committees

It is the responsibility of the sponsor to obtain and maintain independent approval from the applicable regulatory authority and a positive opinion from the competent ethics committees to conduct the study in accordance with local legal requirements, statutes and the European Clinical Trial Directive.

Indemnity insurance will be contracted for the trial subjects in accordance with the applicable local law.

For Germany, the sponsor names the "Leiter der klinischen Prüfung" (LKP) who has to be a physician with at least 2 years' experience in the conduct of clinical trials of drugs according to § 4 (25) and § 40 (1) No. 5 AMG.

11.3.2 Notification of the study

The sponsor is responsible to notify competent regional authority about the study and all investigators of the participating investigational sites, if applicable to local law.

11.3.3 Report and documentation obligation

The sponsor and the investigator are responsible to comply with the report and documentation obligations in accordance with local legal requirements, statutes and the European Clinical Trial Directive.

12 Conditions for Modifying the Protocol

Protocol modifications to ongoing studies must be made via amendment. The sponsor is responsible to obtain independent approval for substantial amendments from the

applicable regulatory authority and a positive opinion from the competent ethics committees in accordance with local legal requirements, statutes and the European Clinical Trial Directive. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects or when the changes are non-substantial and involve only logistical or administrative aspects of the trial (e.g. change of telephone numbers).

13 Study Documentation, eCRFs and Record-Keeping

13.1 Investigator's Files / Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories Investigator's Study File, and patient data.

The Investigator's Study File will contain all essential documents as the protocol / amendments, patient information and informed consent form, Ethics Committee and regulatory authority approval, notification of the federal regulatory authority and competent regional authorities, if applicable, drug records, staff curriculum vitae and authorization forms and other appropriate documents / correspondence etc.

Patient data include patient hospital/clinic records (e.g. medical reports, OP reports appointment book, medical records, pathology and laboratory reports, ECG, EEG, X-ray, etc.) and signed informed consent forms and patient screening and eligibility screening forms.

The investigator must keep these two categories of documents on file for at least 10 years (or more as legally required) after completion or discontinuation of the study. The documents must be archived in a secure place and treated as confidential material.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit.

Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

All documents must be archived in a secure place and treated as confidential material.

13.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when Case Report Forms are illegible or when errors in data transcription are suspected. In case of special problems and / or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected. According to the standards of the data protection law, all data obtained in the course of a clinical study must be treated with discretion in order to guarantee the rights of the patient's privacy.

13.3 Audits and Inspections

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the sponsor may conduct site visits to institutions participating to protocols. The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the sponsor, national regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including eCRFs, source documents, hospital subject charts and other study files) to these authorized individuals. The investigator must inform the sponsor immediately in case a regulatory authority inspection would be scheduled. If inspections will be performed in particular for this study by the competent authority, the competent authority / investigator has to send the inspection report to the sponsor within 5 working days.

13.4 Electronic Case Report Forms (eCRF)

For each patient enrolled, an eCRF must be completed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-

limiting adverse event, thorough efforts should be made to clearly document the outcome.

14 Monitoring the Study

The monitor has the responsibility to familiarize the investigator(s) and the entire center staff involved in the study with all study procedures including the administration of study drug.

The Sponsormust provide a trained monitor to assist the investigator(s) in conducting the clinical study. The monitor must visit the clinical study center before the first patient has been enrolled (initiation visit); at routine monitoring visits during the course of the study at least once if patients were enrolled at the study center; and at study completion. The monitor has the responsibility of reviewing the ongoing study with the investigator(s) to verify adherence to the protocol and to deal with any problems that arise. At all times Sponsor must maintain the confidentiality of the study documents. It is the responsibility of the study monitor to verify the study documents against the patient's original medical records.

The investigator (or his / her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15 Confidentiality of Trial Documents and Patient Records

The investigator and the sponsor (or designee) must assure that according to the standards of the data protection law, all data obtained in the course of a clinical study must be treated with discretion in order to guarantee the rights of the patient's privacy. Patient related documents must be submitted to the sponsor in a pseudonymous manner. The investigator should keep a patient identification log showing codes and names. The investigator should maintain documents not for submission to Sponsor, e.g., patients' written consent forms, in strict confidence.

16 Study Report and Publication Policy

This study will be entered into a clinical trial protocol registry and clinical results database. The sponsor is responsible for the timely reporting of study data. An integrated clinical study report (CSR) has to be completed one year after end of the study (whether completed or prematurely terminated). The report has to be approved by the responsible specialist chosen by the sponsor the statistician and the coordinating investigator / LKP by provision of their signatures. Any publications of the results, either in part or in total (abstracts in journals, oral presentations, etc.) by

investigators or their representatives will require pre-submission-review by the Sponsor and the coordinating investigator / LKP. The coordinating investigator will be given the choice to be the first or the last author for the main publication.

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18 Appendices

18.1 Appendix 1 – ECOG Performance Status

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

18.2 Appendix 2 – RECIST 1.1

According to:

New response evaluation criteria in solid tumors:
Revised RECIST guideline (version 1.1)

Eisenhauer EA, Therasse P, Bogaerts J et al. European Journal of Cancer 45 (2009): 228-247


RECISTGuidelines 1.1.pdf

18.3 Appendix 3 - Junker criteria for tumor regression grading

Differentiation between spontaneous and therapy induced regression as well as the degree of therapy induced regression is critical for assessment of the primary endpoint of this trial.
Since macroscopic examination of the resection does now allow for unequivocal differentiation between vital tumor tissue and therapy induced regression, regions with likely vital tumor tissue or former, now regressively altered, tumor tissue as well as all resected mediastinal lymph nodes should be embedded in paraffin.
If macroscopically unequivocally viable tumor tissue is found, representative section through the tumor (1 FFPE block per cm) will be sufficient. In all other cases the tumor should be embedded fully and all blocks are to be submitted to central review.
The central review process will look for key histological parameters of therapy induced tumor regression:

- Type and extent of the vital tumor tissue
- Degree of tumor necrosis
- Reactive alterations with foam cell reaction
- Fibrosis or scar formation.

To differentiate between small remaining tumor cell infiltrates from reactive histiocytic proliferations and reactive pneumocyte hyperplasia additional immune histochemical analyses such as CK7, Ki-67 and P53 may be needed.

The findings will be classified according to the following regression grading:

Regression grading stages	**Histological observations**
Grade I	No tumor regression or only spontaneous tumor regression in the sections of the primary tumor and mediastinal lymph nodes.
Grade IIa	Morphological signs of therapy-induced tumor regression in the sections of the primary tumor and/or mediastinal lymph nodes in the sections of the primary tumor and/or mediastinal lymph nodes: **More than 10% vital tumor tissue**
Grade IIb	Morphological signs of therapy-induced tumor regression: **Less than 10% vital tumor tissue**
Grade III	Complete tumor regression, no evidence of vital tumor in the sections of the primary tumor and/or mediastinal lymph nodes:
Regression grades IIb and III suggest a good response to neoadjuvant therapy.	

Reproduced from Junker et al. 2001 [12].

18.4 Appendix 4 – Cockcroft-Gault Formula

$$\text{Calculated } CL_{CR} \text{ (ml/min)} = \frac{[(140 - \text{subject's age in years}) \times \text{subject's actual body weight in kilograms}]}{72 \times \text{subject's serum creatinine (in mg/dL)}} *$$

*: x 0.85 for females

$$\text{Calculated } CL_{CR} \text{ (ml/min)} = \frac{[(140 - \text{subject's age in years}) \times \text{subject's actual body weight in kilograms}] \times K^*}{\text{subject's serum creatinine (in µmol/L)}}$$

K*: 1.23 for males, 1.05 for females

18.5 Appendix 5 – NCI-CTC Version 4.03 (CTCAE v4.03)

NCI-CTC Version 4.03

18.6 Appendix 6 – Declaration of Helsinki, Republic of South Africa, October 1996

Declaration of Helsinki

18.7 Appendix 7 – Summary of Changes

The following table provides a summary of changes to the Clinical Study Protocol version 5.0 (02-SEP-2020), which are included in version 4.0 (26-NOV-2018). Minor editorial changes have also been made but are not included in this summary table.

Summary of changes to previous protocol version

Section number	Section title	Version 4.0	Version 5.0 (Changes / additions in ***bold italic*** and deletions as strikethrough)	Type of change and justification for changes
---	**Synopsis** page 7 Inclusion Criteria	11. d. INR 1.4 and PTT < 40 seconds during the last 7 days before therapy	11. d. INR < 1.4 and PTT < 40 seconds during the last 7 days before therapy	**Change: non-substantial** **Justification:** Alignment with section 4.2
---	**Synopsis** page 12 Inclusion Criteria	Study plan FPI Q3/2017 LPI after approx. 18 month LPO after approx. 22 month EoS (after 24 month FU of LPO) after approx. 46 month	Study plan FPI Q2/2018 LPI after approx. 36 month (Q2/2021) LPO after approx. 40 month (Q4/2021) EoS (after 24 month FU of LPO) after approx. 64 month (Q4/2023)	**Change:** non-substantial **Justification:** Adjustment, trail recruitment
3.7 Study	**Inclusion Criteria**	Study plan FPI Q3/2017	Study plan FPI Q2/2018	**Change:** non-substantial **Justification:**

Section number	Section title	Version 4.0	Version 5.0 (Changes / additions in ***bold italic*** and deletions as strikethrough)	Type of change and justification for changes
Duration	page 38 / 39	LPI after approx. 18 month LPO after approx. 22 month EoS (after 24 month FU of LPO) after approx. 46 month	LPI after approx. 36 month (Q2/2021) LPO after approx. 40 month (Q4/2021) EoS (after 24 month FU of LPO) after approx. 64 month (Q4/2023)	Adjustment, trail recruitment