Statistical Analysis Plan
Main Analysis and Addendum Analysis

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

Protocol: NEOMUN

Confidential

Sponsor: AIO-Studien-gGmbH

Table of Contents

List of Abbreviations

AE	Adverse event
CEA	Carcinoembryonic antigen
CI	Confidence interval
CSP	Clinical study plan
CTCAE	Common terminology criteria for adverse events
Cyfra 21-1	Cytokeratin-fragment 21-1
DFS	Disease-free survival
DLCO	Diffusion capacity of lung for CO
DRM	Data review meeting
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FEV	Forced expiratory volume
FU	Follow-up
IMP	Investigational medicinal product
ITT	Intent-to-treat
LD	Least diameter
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OA	Overall
OS	Overall survival
PP	Per-protocol
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SB	Single breath method
SD	Standard deviation
SOC	System organ class
SUV	Standardized uptake value
TL	Target lesion
TLFs	Tables, listings and figures
VA	Alveolar volume
VC	Vital capacity

1. OVERVIEW

1.1 Study Objectives

1.1.1 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.

1.1.2 Secondary Objectives

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

1.1.3 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

1.2 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.

1.3 Endpoints

1.3.1 Primary Endpoint

- Frequency and severity of AEs 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]) (analysis of this end point is not covered in this SAP)

  Pathologic response parameters:
  - Pathologic regression grading according to Junker criteria (see Appendix 3 of CSP)

1.3.2 Secondary Endpoints

- disease free survival
- overall survival

1.3.3 Exploratory Endpoints

Following exploratory endpoints were defined for this study, but will not be covered by this SAP:

- 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

1.4 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.

1.5 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. .				
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.

2. GENERAL CONSIDERATIONS

2.1 Conduct of Analysis

Two analyses will be performed for this study.

- Main analysis will be performed after all patients had their end of treatment, data entry for all visits except the follow-up visits is complete, data were cleaned, a Data Review Meeting was performed and database snapshot has been completed.
- Addendum analysis will be performed after last patient completed the entire study, follow-up data entry and cleaning are complete and database was closed.

Main analysis will summarize all data recorded up to the time of the database snapshot. Addendum analysis will only present data captured during follow-up. This means, the addendum analysis may only include overall survival, end of study details and subsequent cancer therapy. An SAE listing will also be prepared to show possible follow-up information of SAEs ongoing after end of treatment.

2.2 Statistical Software and Quality Control

All statistical analyses will be performed using SAS® version 9.3 or higher. Tables, figures and data listings will be generated in Microsoft® Word® as well as PDF® format.

Quality control of SAS® programs will include a review of the whole process of result generation:

- Review of all analysis SAS® programs
- Review of SAS® log for errors, warnings and other notes that could indicate mistakes in the programs
- Review of all tables, listings and figures for completeness and correctness

2.3 Applicable Standard Operating Procedures

The applicable Standard Operating Procedures (SOPs) of Assign DMB for this study are:

STAT01 Statistical Analysis File

STAT03 Statistical Analysis Plan

STAT04 Interim Analysis

STAT06 Data Review Meeting

STAT07 Report Writing

SAS01 SAS General Principles

SAS04 Handling of Statistical Analyses

2.4 Blinding and Randomization

As it is an open-label and single arm study, principles of blinding and randomization are not applicable.

2.5 Descriptive Analyses

- Descriptive analyses of continuous variables (summary statistics) will be described with the number of non-missing observations, arithmetic mean, standard deviation (±SD), median, quartiles (Q1 and Q3) and range (minimum and maximum).
- Categorical variables (frequency statistics) will be described with the number of non-missing observations and percentages (%).

2.6 Inferential Analyses

Inferential analysis for efficacy is described in Section 5.3. Inferential analysis for safety is described in Section 6.2.3.

2.7 Center and Country Effect

Since this study is a one-center pilot study, stratification by country or study site is not applicable.

2.8 Handling Missing Data

In general, missing data will not be imputed and analysis is restricted on available data, with the following exceptions:

- For time-to-event endpoints (DFS, OS), incomplete dates will be handled as described in Section 5.2.
- Response rates will consider missing response assessments as described in Section 5.2.
- Missing causality assessment for adverse events will lead to handling of the AE as related (see Section 7.3 of the CSP)

2.9 Protocol Deviations

Potential protocol deviations will be collected prior to database snapshot for the main analysis. Potential protocol deviations will be discussed in a data review meeting (DRM) prior to database snapshot for the main analysis and will be classified as relevant or not relevant. A protocol deviation will be considered relevant if it has a potential influence on the efficacy analysis. Relevant protocol deviations will lead to exclusion from the PP Population.

Relevant protocol deviations can be one of the following but are not limited to:

- at least one of the major inclusion criteria was not met (criteria with relevant impact on efficacy)
- at least one of the major exclusion criteria was fulfilled (criteria with relevant impact on efficacy)
- administration of prohibited therapies during the screening and treatment phase as defined in the CSP
- administration of no study treatment
- no documentation of tumor assessment after start of study treatment
- erroneous dose of study medication

2.10 Medical Coding

All information regarding the medical coding of medical history and adverse events can be found in the coding guideline.

2.11 Analysis Populations

2.11.1 Intent-to-Treat population

The Intent-to-Treat (ITT) Population includes all enrolled. A patient is regarded as enrolled if considered eligible for treatment start at screening (i.e. eCRF question “Have all screening assessments been performed and is patient considered eligible for treatment start” is answered with yes by the investigator).

2.11.2 Per-Protocol population

The Per-Protocol (PP) Population will comprise all patients of the ITT population who had no protocol deviation relevant for efficacy evaluation. PP Population will be defined in the DRM performed before the main analysis. For definition of relevant protocol deviations, see Section 2.9.

2.11.3 Safety population

The safety population consists of all patients who received at least one dose of study medication.
If the Safety and ITT Population are identical (i.e. all enrolled patients received at least one dose of treatment medication) the analysis will be performed for the Safety Population and the ITT Population together, labelled with “Safety/ITT Population”.

2.12 Patient Data Listings

All recorded patient data of eligible patients will be included in by-patient data listings. Safety data listings will be restricted to the safety population (treated patients).
Data listings will include the patient number as identifier (and parameter and/or time point if available). A column indicating if a patient is in the PP Population will be shown in all baseline and efficacy listings.

2.13 Table Columns

All analysis tables will include one column including all patients of the respective analysis population.

2.14 Changes in the Conduct of the Study or Planned Analysis

The following changes as compared to descriptions in the CSP are described in this SAP:

- According to a sentence in the CSP, all patients' data is included in data listings. During SAP review it was decided to not include screening failure data in all data listings.
- The CSP planned to include statistical tests between time points. During SAP review it was decided to omit such tests due to small sample size.

3. OVERALL STUDY INFORMATION

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings:

- Patient overview
  - Eligible patients
  - Study populations
  - Screening completion / screening failures incl. reason
  - End of treatment incl. reason
  - End of study incl. reason for study end
- Attended visits

The following information will be provided only in data listings:

- Violated inclusion/ exclusion criteria
- Protocol deviations

4. BASELINE EVALUATION

Baseline characteristics will be summarized for ITT and PP Population, respectively.

4.1 Data Points

- Demographics and baseline characteristics (Age, gender, race, body weight and height, smoking status)
- Disease history
  - Cancer history
  - Histological type
  - Previous cancer treatment (any)
- Medical history by SOC and PT

The following information will be provided only in data listings:

- Concomitant medication
- Concomitant procedure

5. EFFICACY ANALYSIS

Efficacy analyses will be performed primarily on the PP Population and will be repeated on the the ITT population.

5.1 Data Points

Following tables and figures will be provided:

- Tumor response at pre-surgery visit
  - Overall response
  - Δ tumor size
- Tumor regression grading stage (according to Junker criteria)
- Kaplan-Meier statistics for disease free survival (DFS)

- Kaplan-Meier statistics for overall survival (OS)
- Tumor staging
- Tumor markers (CEA, Cyfra 21-1)
- Lung function
    - forced expiratory pressure in 1 second (FEV1)
    - maximum vital capacity (VC MAX)
    - forced vital capacity (FVC)
    - inspiratory vital capacity (VC IN)
    - diffusion capacity of lung for CO (DLCO SB)
    - diffusion capacity of lung for CO / alveolar volume (DLCO/VA)
    - DLCOc SB
    - DLCOc/VA
    - forced expiratory pressure in 1 second / maximum vital capacity (FEV1 % VC MAX)
    - partial pressure of O2 (pO2)
    - partial pressure of CO2 (pCO2)

Corresponding details on the patient-level will be listed.

The following information will be provided only in data listings:

- Screening tumor assessment
- Target lesions
- Non-target lesions
- Translational research
- Survival status

5.2 Definitions

- Disease-free survival (DFS) will be defined as the time length from the date of surgery to the date of tumor recurrence or death (tumor recurrence as reported on follow-up pages in the eCRF, death as reported in the end of study page in the eCRF). Patients that had no tumor recurrence and did not die will be censored at the date of last contact when patient was alive (as reported on the end of study page in the eCRF).
- Overall survival (OS) will be calculated as the time length from the date of surgery to the date of death. Patients that did not die will be censored at the date of last contact when patient was alive (as reported on the end of study page in the eCRF).
- For both DFS and OS the following rule will be applied for incomplete dates: The date of surgery is assumed to always be completely known (day, month and year available), otherwise DFS and OS will not be calculated. For the end dates (death, tumor recurrence, last date patient was alive) patients will be secured at the earliest possible date. E.g. if the date of death is "UK/05/2019" then the patient is censored at 01/05/2019 and thus being considered event-free until this date and status is considered unknown after

this date. If this rule results in negative survival time, the patient is not considered for Kaplan-Meier analysis.

- Δ tumor size will be defined as the difference [mm] between "current SUM LD" and "baseline sum LD" on the tumor response assessment page of the eCRF.

5.3 Inferential Analysis

No statistical tests are performed due to the small sample size.

DFS and OS will be described by means of Kaplan-Meier method. Estimates of median DFS and OS rates for specific time points (at e.g. 12, 24 and 36 months) will be provided with the associated 95% confidence limits.

6. SAFETY ANALYSIS

Safety analyses will be performed for the Safety population.

6.1 Extent of Exposure

Detailed information on study drug administration will be provided in data listings.

6.2 Adverse Events

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings.

6.2.1 Data Points

- Adverse Event Overview
  - Any AE
  - Any AE of clinical interest
  - Any related AE
  - Any severe AE
  - Any AE grade 2-4
  - Any related severe AE
  - Any related AE grade 2-4
  - Any SAE
  - Any related SAE
  - Any AE requiring study treatment dose modification
  - Any AE requiring study treatment discontinuation
- Adverse Events by maximum severity
  - Any AE
  - Any related AE
- Adverse Event by highest relationship
  - Any AE
  - Any AE grade 2-4

- Any SAE

- Adverse Events by SOC and preferred term
  - Any AE
  - Any related AE
  - Any AE grade 2-4
  - Any related AE grade 2-4
  - Any SAE
  - Any related SAE
  - Any AE requiring study treatment discontinuation

6.2.2 Definition

- Severe AE: AEs with severities of Grade 3-5 (severe or medically significant, severe or life threatening, death) will be considered as severe AEs
- Missing causality assessment for adverse events will lead to handling of the AE as "related", see Section 7.3 of the CSP.

6.2.3 Inferential Analysis

AE summary tables will provide the number and percentage of patients with AEs and the 95 % confidence intervals for the event rates according to Wilson.

6.3 Laboratory Parameters

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings.

6.3.1 Data Points

- Hematology
  - basophils absolute
  - eosinophils absolute
  - erythrocytes
  - hemoglobin
  - leukocytes
  - lymphocytes absolute
  - monocytes absolute
  - neutrophils absolute
  - platelets
- Clinical chemistry and coagulation
  - ALT
  - AST
  - activated partial thromboplastin time
  - albumin absolute
  - calcium
  - creatinine
  - creatinine clearance
  - LDH
  - magnesium
  - phosphate
  - potassium
  - prothrombin time relative
  - sodium

- TSH
- total bilirubin
- free T3
- free T4

The following variables will be analyzed descriptively:

- Absolute values by time point
- Absolute change from screening values by time point
- Values above and below normal range by time point

Conversion of laboratory parameters will be performed from a study site specific laboratory unit into the unit to be used in the statistical analysis via the following formula:

- Value in analysis unit = value in study site specific unit * conversion factor

The following units will be used as standard units:

Parameter	Unit used for Analysis
Clinical chemistry and coagulation	
ALT	U/l
AST	U/l
albumin absolute	g/l
calcium	mmol/l
creatinine	mg/dl
creatinine clearance	ml/min
LDH	U/l
magnesium	mmol/l
phosphate	mmol/l
potassium	mmol/l
prothrombin time relative	%
sodium	mmol/l
TSH	mU/l
total bilirubin	mg/dl
free T3	ng/l
free T4	ng/l
Tumor marker	
CEA	µg/l
Cyfra 21-1	µg/l

Parameter	Unit used for Analysis
Clinical chemistry and coagulation	
ALT	U/l
AST	U/l
albumin absolute	g/l
calcium	mmol/l
creatinine	mg/dl
creatinine clearance	ml/min
LDH	U/l
magnesium	mmol/l
phosphate	mmol/l
potassium	mmol/l
prothrombin time relative	%
sodium	mmol/l
TSH	mU/l
total bilirubin	mg/dl
free T3	ng/l
free T4	ng/l

6.4 Other Safety Parameters/ Clinical Assessments

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings.

6.4.1 Data Points

- ECOG status
- Vital signs
    - blood pressure
    - heart rate
    - body temperature
    - body weight

The following information will only be provided in data listings:

- Pregnancy test (if applicable)
- Physical examination
- Quality of life
- ECG
- Chest X-Ray
- Subsequent cancer therapy

7. LIST OF TABLES, DATA LISTINGS AND FIGURES

Numbering of tables, listings and figures will follow principles as below:

- Tables and figures numbering will begin with number 14, listings with number 16.2.

Numbering of Tables (digits after tables/figures prefix):

- First digit will indicate information type shown (1= overall, 2= baseline, 3= efficacy, 4= safety)
- Second digit will represent table/listing/figure type.

7.1 List of Tables

7.1.1 Overall Study Information

No	Legend	Content
14.1.1	Patient overview (All patients)	• Eligible patients • Study Populations (ITT, PP, Safety) • Screening completion / screening failures incl. reason • End of study incl. reason for study end
14.1.2	Attended visits (ITT Population)	

7.1.2 Baseline Evaluation

No	Legend	Content
14.2.1	Demographics and baseline characteristics (ITT Population)	• Age at informed consent • Gender • Race • Body weight and height • Smoking status
14.2.2	Disease history (ITT Population)	• Cancer history • Histological type • Previous cancer treatment (any)
14.2.3	Medical history by System Organ Class and Preferred Term (ITT Population)	
14.2.4-6	Tables 14.2.1-3 will be repeated for the PP Population.	

7.1.3 Efficacy Analysis

No	Legend	Content
14.3.1	Tumor Response at Pre-Surgery Visit (PP Population)	• Overall response • Δ tumor size
14.3.2	Tumor Regression Grading Stage (PP Population)	
14.3.3	Kaplan-Meier Statistics for Disease-Free Survival (PP Population)	
14.3.4	Kaplan-Meier Statistics for Overall Survival (PP Population)	
14.3.5	Tumor Staging (PP Population)	• Tumor stage
14.3.6	Tumor Marker Values Over Time (PP Population)	• CEA • Cyfra 21-1
14.3.7	Tumor Marker Value's Change from Baseline (PP Population)	• CEA • Cyfra 21-1

14.3.8	Lung function test results (PP Population)	• VC MAX • FVC • VC IN • FEV1 • FEV 1% VC MAX • DLCO SB • DLCO/VA • DLCOc SB • DLCOc/VA • pCO2 • pO2
14.3.9-16	Tables 14.3.1-8 will be repeated for the ITT Population.	

7.1.4 Safety Analysis

No	Legend	Content
Adverse Events		
14.4.1	Adverse Events Overview (Safety Population)	• Any AE • Any AE of clinical interest • Any related AE • Any severe AE • Any AE grade 2-4 • Any related severe AE • Any related AE grade 2-4 • Any SAE • Any related SAE • Any AE requiring treatment discontinuation • Any AE requiring treatment dose modification
14.4.2	Adverse Events by Maximum Severity (Safety Population)	• Any AE • Any related AE
14.4.3	Adverse Event by Highest Relationship (Safety Population)	• Any AE • Any AE grade 2-4 • Any SAE
14.4.4	Adverse Events by SOC and Preferred Term (Safety Population)	• Any AE • Any AE grade 2-4 • Any related AE • Any related AE grade 2-4 • Any SAE • Any related SAE • Any AE requiring study treatment discontinuation
Laboratory Parameters		
14.4.5	Hematology Values over Time (Safety Population)	
14.4.6	Hematology Value's Change from Baseline (Safety Population)	
14.4.7	Hematology Values above and below Normal Range by Time Point (Safety Population)	
14.4.8	Clinical Chemistry and Coagulation Values over Time (Safety Population)	
14.4.9	Clinical Chemistry and Coagulation Value's Change from Baseline (Safety Population)	

14.4.10	Clinical Chemistry and Coagulation Values above and below Normal Range by Time Point (Safety Population)	
Other Safety Parameters		
14.4.11	ECOG Status (Safety Population)	
14.4.12	Vital Signs (Safety Population)	• Blood pressure • Heart rate • Body temperature • Body weight

7.2 List of Data Listings

7.2.1 Overall Study Information

No	Legend	Content
16.2.1.1	Patient Overview (All patients)	Patient ID, Date of written informed consent, Version of informed consent, Version of informed consent form, Patient eligible, Reason not eligible, Planned date of treatment start, ITT population, PP population, Safety population
16.2.1.2	Attended visits (ITT Population)	Patient ID, Visit, Planned date of visit, Actual date of visit, Days between planned and actual date, Reason outside time window, Days between Visit 1 and Discharge
16.2.1.3	End of study details (ITT Population)	Patient ID, Date of study end, Date of last contact when patient was alive, Reason for study end, Specification lost to FU/other reason, Death date, Primary cause of death, Date of pregnancy noticed, Pregnancy status
16.2.1.4	Violated Inclusion/ Exclusion Criteria (ITT Population)	Patient ID, Criterion category, Criterion, Answer
16.2.1.5	Protocol violations (All patients)	Patient ID, Protocol deviation category, Protocol deviation description, Classification, Reason for classification

7.2.2 Baseline Data

No	Legend	Content
16.2.2.1	Demographics and baseline characteristics (ITT Population)	Patient ID, Gender, Year of birth, Age at informed consent, Body height, Body weight, Race, Childbearing potential, Reason no childbearing potential, Smoking status, Prev. smoker duration abstinence [years], Total tobacco consumption [pack years]
16.2.2.2	Cancer history (ITT Population)	Patient ID, Any cancer history within 5 years prior to screening, Specification, Any treatments of previous cancer, Number of previous cancer treatments
16.2.2.3	Previous cancer treatment details (ITT Population)	Patient ID, Type of prior treatment, Start date of prior treatment, Stop date of prior treatment, Location/ description
16.2.2.4	Tumor diagnosis (ITT Population)	Patient ID, Date of first NSCLC diagnosis, NSCLC location, Histologically/ cytologically confirmed NSCLC, Date of initial biopsy, Date of confirmation, Method, Histological type

16.2.2.5	Imaging date and time at screening (ITT Population)	Patient ID, PET/CT performed, Date of PET/CT, MRI brain performed, Date of MRI brain
16.2.2.6	Medical History (ITT Population)	Patient ID, MH number, Condition, Start date, End date/ ongoing, Treated with medications at screening, Start date unknown - prior to IC, End date unknown - prior to IC
16.2.2.7	Prior/ Concomitant Medications (ITT Population)	Patient ID, CM number, Medication (trade name preferred), Start Date, Start date unknown but prior IC, End Date/ ongoing, Single-dose and unit, Frequency, Route of Administration, Indication
16.2.2.8	Prior/ Concomitant Procedures (ITT Population)	Patient ID, CP number, Procedure, Start Date, Start date unknown but prior IC, End Date/ ongoing, End Date unknown but prior IC, Indication

7.2.3 Efficacy Data

No	Legend	Content
16.2.3.1	Screening Tumor Assessment (ITT Population)	Patient ID, Visit, Date of assessment, Number of target lesions, Current sum LD [mm], Current sum LD present, Number of non-target lesions,
16.2.3.2	Tumor Response at Pre-Surgery Visit (ITT Population)	Patient ID, date of assessment, Any new lesions, New lesion location, New lesion present, Date of progression, Current sum LD [mm], Current sum LD present, Baseline sum LD [mm], Δ tumor size, Target lesion response calculated, Target lesion response investigator, Reason inconsistent (TL response), Non-target lesion response, Non-target lesion response present, Overall response calculated, Overall response investigator, Reason inconsistent (OA response)
16.2.3.3	Target Lesion Details (ITT Population)	Patient ID, Visit, Target lesion, Location, Description of location, Method, Diameter [mm], Lesion present, Lesion too small to measure, Lesion diameter (calculated) [mm]
16.2.3.4	Non-Target Lesion Details (ITT Population)	Patient ID, Visit, Non-Target lesion(s), Location, Number of lesion(s), Description of location, Method, Lesion(s) still present, Lesion(s) not assessed
16.2.3.5	Histology (ITT Population)	Patient ID, Tumor regression grading performed, Date tumor regression grading, Regression grading stage, Reason regression grading not performed, Tumor size (largest diameter) [mm], Histologic subtype, Adenocarcinoma subtype
16.2.3.6	Overall Response (ITT Population)	Patient ID, OS [months], OS censored, DFS [months], DFS censored
16.2.3.7	Tumor Staging (ITT Population)	Patient ID, Visit, Stage identifier, Stage
16.2.3.8	Tumor Markers (ITT Population)	Patient ID, Visit, Has blood sample been drawn, Date of sample drawn, Actual age [years], Parameter, Value, Unit, Clinically relevant, Causal relationship
16.2.3.9	Lung Function (ITT Population)	Patient ID, Visit, Lung function test, Test performed, Date test performed, Method, Parameter, (Best) Value, Unit ((Best) value), Best/target value [%]

16.2.3.10	Translational research (ITT Population)	Patient ID, Visit, Blood sample for biomarkers drawn, Date of blood sample drawn
16.2.3.11	Survival status/ Follow-up (ITT Population)	Patient ID, Visit, Patient alive, Tumor recurrence, Date of diagnosis, CT thorax scan performed, X-ray performed

7.2.4 Safety Data

No	Legend	Content
16.2.4.1	Extent of Exposure (ITT Population)	Patient ID, Visit, Pembrolizumab administered, Reason not administered, Start date, Start time, End date, End time, Duration of administration [min], Reason duration outside time window, Dose according to protocol (200 mg), Dose [mg], Reason dose not per protocol
Adverse Events		
16.2.4.2	Any Adverse Events (Safety Population)	Patient ID, AE count, AE term, Event description, System organ class, Preferred Term, Start date, Stop date, Event of clinical interest, Serious AE, Specification of SAE, Date of becoming serious, CTCAE grade, Causal relationship to study drug, Action taken (IMP), Action taken (other), Outcome
16.2.4.3	Severe Adverse Events (Safety Population)	See table 16.2.4.2
16.2.4.4	Adverse Events of Grade 2-4 (Safety Population)	See table 16.2.4.2
16.2.4.5	Serious Adverse Events (Safety Population)	See table 16.2.4.2
16.2.4.6	Related Adverse Events (Safety Population)	See table 16.2.4.2
16.2.4.7	Related Severe Adverse Events (Safety Population)	See table 16.2.4.2
16.2.4.8	Related Adverse Events of Grade 2-4 (Safety Population)	See table 16.2.4.2
16.2.4.9	Related Serious Adverse Events (Safety Population)	See table 16.2.4.2
16.2.4.10	Adverse Events of Clinical Interest (Safety Population)	See table 16.2.4.2
16.2.4.11	Adverse Events Requiring Study Treatment Dose Modification (Safety Population)	See table 16.2.4.2
16.2.4.12	Adverse Events Requiring Study Treatment Discontinuation (Safety Population)	See table 16.2.4.2
Laboratory Parameters		
16.2.4.13	Laboratory Normal Ranges	Parameter, Lower Limit Normal (female), Upper Limit Normal (female), Lower Limit Normal (male), Upper Limit Normal (male), Unit, Valid from date (inclusive), Valid from age (inclusive)
16.2.4.14	Hematology Values (Safety Population)	Patient ID, Visit, Blood sample drawn, Date sample drawn, Parameter, Value, Unit, Change from baseline, Lower limit, Upper limit, Outside normal range, Clinically relevant, Causal relationship
16.2.4.15	Clinical Chemistry and Coagulation Values (Safety Population)	See Listing 16.2.4.14
Other Safety Parameters		
16.2.4.16	Surgeries performed (Safety Population)	Patient ID, Surgery performed, Date of surgery, Method, Approach, Extensions, Systematic lymph node dissection performed, Intraoperative blood loss [ml], Intraoperative blood transfusion

		performed, Post-operative complications, Length of ICU stay, Re-admission to ICU, Date of re-admisson
16.2.4.17	Vital signs (Safety Population)	Patient ID, Visit, Parameter, Value, Unit
16.2.4.18	Cardiac evaluation (Safety Population)	Patient ID, Visit, Evaluation performed, Cardiac evaluation, Date, Result, Specification of abnormality
16.2.4.19	ECOG performance status (Safety Population)	Patient ID, Visit, Date ECOG Score, ECOG Score
16.2.4.20	Routine Chest X-Ray (Safety Population)	Patient ID, Visit, Chest X-Ray performed, Date of performance, Tumor visible, Comments
16.2.4.21	Pregnancy test (Safety Population)	Patient ID, Visit, Pregnancy test performed, Date of test, Reason not performed, Method, Result
16.2.4.22	Quality of Life (Safety Population)	Patient ID, Visit, Date of assessment, Quality of Life question, Answer/Result