Clinical Trial Protocol

	Document Number:	**c13055147-03**
EudraCT No.: **EU Trial No:**	2016-005042-37	
BI Trial No.:	1200.283	
BI Investigational Product(s):	Afatinib in combination with pembrolizumab	
Title:	LUX-Lung IO: A phase II, open label, non-randomised study of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous cell carcinoma of the lung	
Lay Title:	A phase II study that tests afatinib in combination with pembrolizumab in patients with squamous cell carcinoma of the lung	
Clinical Phase:	II	
Trial Clinical Monitor:	Phone: / Fax:	
Coordinating Investigators:		
Status:	Final Protocol (Revised Protocol (based on global amendment 2)	
Version and Date:	**Version: 1.0** **Version: 2.0** **Version: 3.0**	**Date: 04 May 2017** **Date: 12 Mar 2019** **Date: 11 Apr 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name:	Boehringer Ingelheim
Finished product name:	Giotrif/Gilotrif
Active ingredient name:	Afatinib + pembrolizumab
Protocol date:	04 May 2017
Revision date:	11 Apr 2019
Trial number:	1200.283
Title of trial:	LUX-Lung IO: A phase II, open label, non-randomised study of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous cell carcinoma of the lung
Coordinating Investigators:	
Trial site(s):	International, multi-centre trial
Clinical phase:	II
Objective(s):	**[Primary Objective]** ▪ To assess the efficacy of afatinib in combination with pembrolizumab, as measured by objective response (OR) in patients with locally advanced or metastatic squamous NSCLC who progressed during or after first line platinum-based treatment **[Secondary Objectives]** ▪ To confirm the Recommended Phase 2 Dose (RP2D), assess the safety profile, and the secondary measures of clinical efficacy including disease control (DC), duration of objective response (DoR), progression free survival (PFS), overall survival (OS), and tumour shrinkage

Methodology:	Open-label, non-randomised, single arm, phase II study. Eligible patients have locally advanced or metastatic squamous NSCLC who progressed during or after first line platinum-based treatment and who are immune checkpoint inhibitor naïve. Prior treatment with EGFR targeted therapy is not allowed
Number of patients entered:	Approximately 60 patients
Number of patients on each treatment:	Approximately 60 patients
Diagnosis:	Locally advanced (stage IIIb) or metastatic (stage IV) squamous NSCLC
Main in- and exclusion criteria:	1. Pathologically confirmed diagnosis of NSCLC considered to be of squamous histology, including mixed histology, in the opinion of the investigator 2. Locally advanced (stage IIIb) or metastatic (stage IV) NSCLC not considered eligible for curative therapy 3. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV SCC of the lung. This includes patients relapsing within 6 months of completing (neo) adjuvant/curative-intent chemotherapy or definitive chemoradiotherapy. Patients should be eligible to receive second line therapy in the opinion of the investigator. 4. At least one target lesion (outside the brain), that can be accurately measured per RECIST v 1.1. In patients who only have one target lesion and a biopsy of the lesion is required; the baseline imaging must be performed at least two weeks after the biopsy 5. Availability and willingness to provide a fresh tumour tissue sample obtained after relapse or progression on or after prior therapy. In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen may be submitted 6. ECOG performance status of 0 or 1 7. Adequate organ function defined as all of the following (all screening labs should be performed within 10 days of treatment initiation):

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelets	≥75 x 10^9/L
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR**	≤ 1.5 x ULN **OR**

<table>
<tr><td></td><td>
<table>
<tr><td>Measured or calculated[a] creatinine clearance (Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl)</td><td>≥50 mL/min for patients with creatinine levels >1.5x ULN</td></tr>
<tr><td colspan="2">Hepatic</td></tr>
<tr><td>Total bilirubin</td><td>≤1.5 times the upper limit of normal (ULN)</td></tr>
<tr><td>AST (SGOT) and ALT (SGPT)</td><td>≤2.5 x ULN OR ≤5 x ULN for patients with liver metastases</td></tr>
<tr><td colspan="2">Coagulation</td></tr>
<tr><td>• International Normalised Ratio (INR) or Prothrombin Time (PT)</td><td>• ≤1.5xULN unless patient is receiving anticoagulant therapy as long as PT is within therapeutic range of intended use of anticoagulants</td></tr>
<tr><td>• Activated Partial Thromboplastin Time (aPTT)</td><td>• ≤1.5xULN unless patient is receiving anticoagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants</td></tr>
<tr><td colspan="2">[a] Creatinine clearance should be calculated per institutional standard</td></tr>
</table>
8. No prior therapy with any immune checkpoint inhibitor or EGFR targeted therapy; however prior (neo) adjuvant checkpoint inhibitor and EGFR-targeted therapy is allowed if completed at least 12 months before relapse
9. No history of (non-infectious) ILD/pneumonitis that required steroids or current ILD/pneumonitis
10. No active infection requiring intravenous systemic therapy</td></tr>
<tr><td>Test product(s):</td><td>Afatinib</td></tr>
<tr><td>dose:</td><td>Safety run in: The starting dose of afatinib is 40 mg once daily in combination with pembrolizumab. In case the RP2D for afatinib is not confirmed as 40 mg, 12 more patients will be included in the safety run in with a starting dose of afatinib 30 mg once daily. In addition, ongoing patients on afatinib 40 mg will have their dose reduced to 30 mg.

Main study part: at RP2D of afatinib 40 mg or 30 mg once daily in combination with pembrolizumab as determined during the safety run in</td></tr>
<tr><td>mode of administration:</td><td>Oral, once daily, continuous</td></tr>
<tr><td>Comparator product:</td><td>Pembrolizumab (given in combination with test product)</td></tr>
<tr><td>dose:</td><td>Fixed dose pembrolizumab: 200 mg once every 3 weeks</td></tr>
<tr><td>mode of administration:</td><td>Intravenous infusion over 30 minutes (25-40 minutes is permitted) once every 3 weeks</td></tr>
<tr><td>Duration of treatment:</td><td>Both afatinib and pembrolizumab will be given until documented disease progression (per RECIST 1.1 and confirmed with irRECIST), or unacceptable adverse events, or other reasons</td></tr>
</table>

	requiring treatment discontinuation, or for up to 35 treatment cycles, which is the approved treatment duration for pembrolizumab monotherapy. In case of early discontinuation of one agent, the other agent may be continued as monotherapy for up to 35 cycles. After study treatment completion, further therapy will be decided by the investigator including continuation of afatinib (using commercial product), alternative therapy, or best supportive care
Endpoints:	**Primary endpoint:** • Objective response (OR)* **Secondary endpoints:** • Disease control (DC)* • Duration of objective response (DoR)* • Progression-free survival (PFS)* • Overall survival (OS) • Tumour shrinkage* • Recommended Phase 2 Dose (RP2D) *By investigator assessment according to RECIST 1.1
Safety criteria:	Intensity and incidence of reported AEs (AEs will be assessed using the US National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) Safety is overseen by a Safety Monitoring Committee (SMC)
Statistical methods:	**Efficacy Endpoints** Efficacy endpoints will be summarised descriptively. For OR and DC the frequency, proportion, and percentage of patients and 95% two-sided confidence interval will be presented. For survival variables, the median survival time and 95% two-sided confidence interval will be presented using the Kaplan-Meier method. Tumour shrinkage measured as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions will be summarised descriptively **Dose confirmation** Dose confirmation is guided by a Bayesian Logistic Regression Model (BLRM) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of the dose confirmation part, the toxicity probability at each dose level will be calculated to determine an estimate of the RP2D

FLOWCHART

	Screening	Cycle1[a]		Cycle 2 and onwards[a]	End of Trial Treatment[b]	End of REP [c]	Follow-up Progression[d]	Follow-up Survival[e]	End of Trial
Visit abbreviation	**SV**	**C1_V1**	**C1_V2**	**Cx_V[f]**	**EOT**	**EOR**	**FU-PDy[g]**	**FU-OSz[h]**	**FV[18]**
Time point	**Day -28 to 0**	**Day 1**	**Day 8 ±2**	**Day 1[i] ±3 of each cycle (every 3 weeks)**	**Day 0-14 after discontinuation of both study medications**	**Day 30-35 after last trial drug**	**Every 9 weeks ± 1 after C1_V1[16]**	**Every 9 weeks ± 2 after last FU**	
Informed Consent[1]	X								
Demographics	X								
Medical History	X								
Review of In-/Exclusion criteria	X[2]								
Safety lab and urinalysis[3]	X[3]	X		X[3]	X	X			
Pregnancy test[4]	X				X				
Thyroid function testing[5]	X			X[5]					
12 Lead ECG[6]	X								
Blood sample for PK analysis[7]				X[7]					
Tumour biopsy[8]	X								
Biomarker blood sampling[9]		X		X[9]	X[9]		X[9]		
Full physical examination[10]	X				X				
Limited physical examination[10]		X		X		X	X		
Vital Signs	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X	X	X		
Concomitant therapy[11]	X	X	X	X	X	X	X		
Adverse events[12]	X	X	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]
Start of treatment		X							
Dispense afatinib		X		X					
Afatinib treatment		Continuous							
Pembrolizumab treatment[13]		Day 1 of each cycle							
Compliance check afatinib[14]			X[14]	X	X				
Termination of trial medication[15]					X				
Tumour assessment[16]	X			X[16]			X[16]		
Vital status[17]						X	X	X	X
Completion of patient participation[18]									X[18]

a All cycles are 21 days in duration. Patients may continue on treatment for up to 35 cycles or until any other criteria for stopping medication are met (see Section 3.3.4.1). C1V1 can be done on the same day as the screening visit only if all screening assessments are completed.

b This refers to completion of study treatment (as scheduled) as well as premature treatment withdrawal. If the decision to permanently discontinue both trial medications is taken during a scheduled visit (also in case afatinib had been taken in the morning prior to the visit), the EOT (End of Treatment) visit should be performed instead of the scheduled visit. The EOT visit must be performed as soon as possible (at latest, within 14 days) after the last study drug administration (afatinib, pembrolizumab, or both whichever is later); however, the individual termination of trial medication eCRF page must be completed when either is discontinued. In case only one trial treatment is discontinued and the other is continued, the Cx_V should be performed instead of the EOT, and the EOT is performed when also the other trial treatment has been discontinued. Please also see Section 3.3.4.1. The imaging schedule should continue as described under footnote 16 and as indicated.

c The EOR (End of Residual Effect Period) visit is performed at least 30 days (30-35 days) after permanent discontinuation of afatinib and pembrolizumab trial treatment. In case only one of the trial treatments is discontinued the patient continues the treatment cycles i.e. Cx_V

d Follow-up for progressive disease (FU-PD) visits are only for patients who have not progressed and/or not started subsequent anti-cancer treatment at EOR. FU-PD visits will take place as per the imaging schedules (see footnote 16) until confirmed PD or start of subsequent anti-cancer treatment. With the early termination of the study, there is no more follow-up for progressive disease after a patient discontinues treatment.

e After documented PD or start of subsequent anti-cancer treatment and EOT and EOR have been completed, patients will enter follow-up for overall survival (FU-OS). No visits will be performed for the purposes of the trial, but data on subsequent anti-cancer treatment and vital status will be collected from medical records or via telephone. The FU-OS period ends when the patient dies, is lost to follow-up, withdraws consent for collection of overall survival data, or completion of the whole trial. With the early termination of the study, there is no more follow-up for overall survival after documented PD or start of subsequent anti cancer therapy.

f x is the number of the treatment cycle.

g y is the number of the follow-up progression assessment, starting with FU-PD1. With the early termination of the study, there is no more follow-up for progressive disease.

h z is the number of the follow-up survival assessment. With the early termination of the study, there is no more follow-up for overall survival.

i Starting at cycle 2, day 1 of each cycle may be postponed for up to 3 days for administrative reason, but 14 days will be accepted when the patient is recovering from an AE. This should not affect the imaging schedule - the patients still have to come in for the tumour assessments based on the date of first drug intake.

1 Written informed consent must be obtained before any protocol specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent to collection of a blood sample for biomarkers is optional and so is the testing for exploratory tumour tissue biomarkers.

2 In-/exclusion criteria should be re-confirmed before treatment start. Lab tests do not need to be repeated if performed within 10 days prior to treatment start and there is no clinical reason to repeat lab tests.

3 All screening labs should be performed or repeated within 10 days prior to treatment initiation; all other screening assessments are performed within 28 days. Re-screening is permitted, if applicable. Refer to Section 5.2.3 for an overview of the clinical laboratory tests. Starting at Cycle 13, lab tests will be performed every other cycle (C13V, C15V, C17V etc, – C35V.). After 35 cycles of trial treatment, lab tests will be performed at EOT, EOR, and as clinically indicated. In case of any elevation of ALT/AST and bilirubin, please see Section 10.5.

4 A pregnancy test is mandatory for female patients of childbearing potential within 72 hours prior to start of treatment and at EOT. Repeat as necessary during the treatment period as required per local regulation (refer to Section 4.2.2.3).

5 Thyroid function testing (TSH, T3, T4) at baseline, every six weeks during treatment with pembrolizumab, and as clinically indicated.

6 ECG is performed at screening and repeated as clinically indicated.

7 Pharmacokinetic (PK) sampling will take place in all patients at Cycle 2 and Cycle 3 before trial drug administration as specified in Section 5.3 and Appendix 10.1.

8 A fresh tumour biopsy (alternatively archived tissue) will be required at screening for central measurement of PD-L1 expression and correlative studies (see also Section 5.4.1). In case a fresh tumour biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern) an archived specimen obtained as part of routine clinical practice prior to treatment initiation may be submitted. A biopsy obtained upon PD after prior therapy for squamous NSCLC can be used. In patients who only have one target lesion according to RECIST 1.1 and a biopsy of the lesion is required, the baseline imaging must be performed at least two weeks after the biopsy. Further exploratory biomarker analyses are optional and are only performed if the patients have given written informed consent for this.

9 Collection of blood samples for blood-born biomarkers is optional and is only performed if the patients have given written informed consent for this. It must be obtained at C1_V1 prior to first drug administration, at C4V, and at the time of PD (either at EOT visit or FU-PD, dependent on the timepoint of PD). Refer to Section 5.4. With the early termination of the study, no blood samples for biomarkers will be collected at the time of PD.

10 Includes height (at screening only) and weight. Refer to Section 5.2.1 for details on complete and limited physical exam procedures.

11 For concomitant therapy and restrictions on concomitant therapy, see Sections 4.2.1.1 and 4.2.2.1.

12 For details on Adverse Event reporting after treatment discontinuation, refer to Sections 5.2.6.2 and 6.2.3. Early and proactive management of side effects is essential for retention and the site should call the patient a few days after starting treatment to discuss whether the patient has side effects and how these can be treated. In addition, a phone call around day 15 is recommended and the patient should be instructed to contact the sites if applicable. All AEs (non-serious and serious and all AESIs) are reported for a minimum of 30 days post permanent discontinuation of the afatinib and pembrolizumab trial treatment. After the end of the REP until the individual subject's end of trial, 90 days after the last dose of pembrolizumab or 30 days following cessation of trial treatment if the patient initiates new anticancer therapy, whichever is earlier, all AESIs related to afatinib and all SAEs are reported. After this time, only related SAEs and AESIs related to afatinib are reported. Information about pregnancy should be collected for female patients of childbearing potential at least up to 120 days after the last dose of pembrolizumab treatment and 2 weeks after last afatinib treatment.

13 Pembrolizumab must be administered on day 1 of each cycle, but a time window of ±3 days will be allowed. Pembrolizumab may be continued for up to 35 cycles, which is the approved treatment duration for pembrolizumab monotherapy. After EOT for individual patient, further therapy will be decided by the investigator including continuation of afatinib (using commercial product), alternative therapy, or best supportive care.

14 After one week on study medication, treatment compliance should be discussed with the patient, to ensure that afatinib is being taken correctly (no compliance calculation is performed). At the end of each 21 day cycle, treatment compliance is calculated and entered in the eCRF.

15 Afatinib and pembrolizumab study treatment combined or as monotherapy is allowed up to 35 cycles if, in the opinion of the investigator, the patient continues to derive clinical benefit, despite the other being discontinued.

16 Tumour assessments should include computed tomography (CT) scans of chest and abdomen and a brain MRI at screening. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, bone) using an appropriate method (CT scan, MRI, or bone scan) should be performed. The same radiographic procedure must be used throughout the study. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray, CT scan, MRI, or bone scan) should be performed and repeated at each tumour assessment (see Appendix 10.3 and Appendix 10.4 for more details). Assessments will be performed at the following time points, irrespective of scheduled visits, until PD and/or start of subsequent anti-cancer treatment for disease:

- Screening visit (within 28 days prior to first drug intake). A scan performed as part of routine clinical practice and prior to provision of informed consent and within the screening timeframe can be used
- During week 9 (56-63 days after C1_V1)
- Every 9 weeks (63 ± 7 days) thereafter until PD or start of subsequent anti-cancer treatment.

After PD per RECIST, repeat imaging for confirmation is required. Repeat imaging ≥4 weeks to confirm In the event of early discontinuation or interruption/delay of treatment the tumour assessment schedule should not be changed. With the early termination of the study, tumour assessment is done per local standard and the timing and methods of imaging should follow local practice until PD, start of subsequent anti-cancer treatment for disease or withdrawal from trial treatment.

17 Vital status (overall survival data) can be collected from the patient notes etc. or by telephone contact with the patient; a formal study visit is not required (see also Section 6.2.3). Exception: In case the patient is still in the EOR/FU or FU-PD, the patient needs to attend trial visits. With the early termination of the study, collection of vital status is no longer necessary.

18 When stopping trial participation, Final Visit (FV) must be completed for all patients who received study medication (see Section 3.3.4). However, a formal study visit is not required.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BLRM	Bayesian Logistic Regression Model
CI	Confidence Interval
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DC	Disease Control
DOR	Duration of Objective Response
EOR	End of Residual Effect Period
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FFPE	Formalin-fixed Paraffin Embedded
FV	Final Visit
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastro Intestinal
IB	Investigator’s Brochure
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
ILD	Interstitial Lung Disease
irAEs	Immune-Related AEs
irRECIST	immune-related RECIST
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Drug Regulatory Activities
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
OPU	Operative Unit
OR	Objective Response

OS	Overall Survival
PFS	Progression Free Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Ligand 1
PK	Pharmacokinetics
p.o.	per os (oral)
PT	Prothrombin Time
RP2D	Recommended Phase 2 Dose
REP	Residual Effect Period, after the last dose of medication with measurable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Squamous cell carcinoma (SCC) represents the second most common histologic subtype of lung cancer (preceded only by adenocarcinoma). In locally advanced unresectable or metastatic disease, doublet chemotherapy regimens (including cisplatin or carboplatin and a third-generation agent such as gemcitabine, taxanes, or vinorelbine) remain the cornerstone of front-line systemic treatment. Genomic alterations in SCC of the lung have not been comprehensively characterised, and no molecularly targeted therapies have been specifically developed for the treatment of this disease.

Molecular data suggest a role for overexpression or gene amplification of EGFR in the pathobiology of SCC. Several studies (R16-5728, R15-2034) suggest that EGFR overexpression is more common in squamous tumours (up to 82% of cases) than in adenocarcinomas. This feature might explain the sensitivity of some patients with SCC of the lung to EGFR-targeted treatments. The LUX-Lung 8 trial comparing afatinib versus the reversible EGFR TKI erlotinib for second-line treatment of patients with squamous NSCLC, showed that afatinib significantly improved progression-free survival (which was the primary endpoint) and key secondary endpoint of overall survival. In addition, longer-term survival at 12 months and 18 months was significantly improved with afatinib. Afatinib was also associated with improvements in objective response (6% versus 3%) and duration of response (7.29 versus 3.71 months), significant improvements in disease control, patient-reported outcomes, and disease-related symptoms compared with erlotinib (P15-06906). Because EGFR mutations are rare (<5%) in SCC of the lung (R15-2035), it is unlikely that the improved survival outcomes observed with afatinib in this study were driven by molecular aberrations of EGFR. These improvements might be a result of afatinib's higher potency and broader irreversible ErbB blockade in this setting compared with EGFR inhibition alone.

The development of immune checkpoint inhibitors has been revolutionary in the field of cancer immunotherapy. Blockade of programmed cell death protein 1 (PD-1) has demonstrated durable responses across different tumour types, including SCC of lung. This led to the approval of three immune checkpoint inhibitors. Of them, pembrolizumab has demonstrated significant improvement in terms of PFS and OS compared to standard of care chemotherapy in both first and second line therapy of patients with PD-L1 expression score ≥50% and ≥1% respectively (R16-4803, R16-0876).

Preclinical evidence suggests that PD-L1 tumour expression may be constitutively driven by EGFR signalling in EGFR mutant NSCLC. Treatment with anti-PD-1 antibodies in preclinical EGFR mutant lung cancer models have demonstrated delayed tumour growth and increased survival (R15-1556). In preclinical cell lines and genetically engineered mouse models (GEMM), EGFR-driven tumours expressed higher levels of PD-L1 with a more immunosuppressive tumour microenvironment (increased FoxP3+ T-cells, decreased CD8+/CD4+ ratio) (R15-1555).

In the clinical setting, a phase I trial combining the anti-PD-1 antibody, nivolumab with erlotinib in patients with EGFR mutant NSCLC, reported an encouraging anti-tumour activity along with a manageable safety profile (R16-0317). The Phase I study examined patients with Stage IIIB/IV EGFR mutant NSCLC who were chemotherapy naive or experienced progression after prior EGFR TKI therapy. Patients received nivolumab 3 mg/kg i.v. Q2W +

erlotinib 150 mg PO daily until progression of disease or unacceptable toxicity. Interim analysis included 21 patients who received treatment for >10 months prior to analysis. Of the 20 patients who had acquired erlotinib resistance, 3 patients showed partial responses. Duration of responses was 6.1+, 16.3+, and 27.1+ weeks. Nine patients (45%) had stable disease and three patients (33%) responded. Similarly, an ongoing phase Ib trial combining full dose erlotinib with atezolizumab (anti PD-L1 antibody) in EGFR mutant NSCLC demonstrated a manageable safety profile (R17-0546). Globally considered, these findings suggest that concurrent inhibition of PD-1 and EGFR pathways may represent a rational and promising approach for EGFR-driven tumours, such as SCC of the lung, to increase response rate and duration of response, and delay development of resistance (R15-1555, R16-5263).

1.2 DRUG PROFILE

For a more detailed description of the afatinib profile please refer to the current Investigator's Brochure (IB) (c01617169-04) and/or local product label information.

Afatinib (BIBW2992) is a small molecule, selective and irreversible ErbB family blocker. In preclinical models it effectively inhibits signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4 resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50 mg. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. The major route of elimination of afatinib was via faeces.

Afatinib is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for $AUC_{0-\infty}$ and C_{max} when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % ($AUC_{0-\infty}$) and 22 % (C_{max}), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators (refer to Section 10.8). In pre-clinical studies afatinib is not irritant to intact skin but an ocular irritant.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (i.v.) immunotherapy for advanced malignancies. (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Refer to the current local product label information and/or to the Summary of Product Characteristics (SmPC) or US Prescribing Information. For more details on specific indications refer to the Investigator brochure c16013985

1.3 RATIONALE FOR PERFORMING THE TRIAL

Although both afatinib and pembrolizumab have demonstrated effect in SCC patient population (in terms of PFS and OS) it remains moderate and more treatment options are needed. This trial is combining both agents which are active in this setting in order to initially assess their tolerability and get indication about the preliminary anti-tumour activity.

To improve patient outcome, it is hypothesised that the combination of afatinib and pembrolizumab can lead to increased response rate with prolonged duration of response. This trial will assess the feasibility of such combination approach in terms of safety and tolerability, and eventually confirm whether it will achieve a better efficacy as compared to either agent alone.

This study aims to confirm the Recommended Phase 2 Dose (RP2D), the safety profile, and the efficacy of afatinib in combination with pembrolizumab in patients with squamous NSCLC, who are progressing during or after first line platinum-based standard therapy without any prior treatment with an immune checkpoint inhibitor or EGFR targeted therapy.

The potential therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on, there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug.

If clinically meaningful efficacy results are observed together with an acceptable safety and tolerability profile, further development of this treatment combination will be considered.

1.4 BENEFIT - RISK ASSESSMENT

Both afatinib and pembrolizumab are approved agents for the treatment of patients with SCC of the lung and the combination of afatinib and pembrolizumab is hypothesised to increase response rate with prolonged duration of response as compared to each monotherapy.

The most common side effects from afatinib treatment are well characterized and include primarily diarrhoea, rash/acne, and stomatitis. For AE details please refer to the IB (c01617169-04). The severity of AEs is dose-dependent and potential side effects can be managed with treatment pauses, dose reductions, and administration of appropriate supportive care measures as described in Section 6.2.3. ILD/pneumonitis or ILD-like events are a known and infrequent risk associated with EGFR inhibitor therapy. Patients with known ILD/pneumonitis are not eligible for inclusion in the trial, and careful monitoring of pulmonary symptoms with sudden onset is warranted during the trial. A Safety Monitoring Committee (SMC) will oversee the trial and an external expert (e.g. ILD expert) may be appointed as needed to adjudicate potential ILD/pneumonitis cases. See Section 1.4.

In KEYNOTE-010, pembrolizumab was well tolerated, with primarily low-grade toxicities, most commonly fatigue, rash, and decreased appetite. Grade 3 or higher toxicities occurred in less than 17% of patients. Sixteen patients (5%) in the low dose level and fifteen patients (4%) in the higher dose level developed pneumonitis, including seven patients (2%) with grade 3 or higher pneumonitis in each dose level, three of whom died (<1% of all patients

treated with pembrolizumab) (R16-0876). Pembrolizumab immune-related events, as described in Section 4.2.3, are usually effectively managed with withholding or discontinuing pembrolizumab and initiating corticosteroid as outlined in the most recent version of the IB (c16013985).

The combination of nivolumab (an immune checkpoint inhibitor) with erlotinib (a 1st generation EGFR TKI) has previously been tested in a phase I trial CheckMate 012 (R16-5545) in patients with EGFR mutation-positive NSCLC, and showed an encouraging anti-tumour activity along with a manageable safety profile (R16-0317). Data from another trial indicated that the combination of full dose erlotinib with atezolizumab (PD-L1 inhibitor) is tolerable in advanced EGFR mutation-positive NSCLC. No new adverse events were identified and safety is similar to that of each agent alone (R17-0546).

In contrast, the combination of the 3rd generation EGFR TKI osimertinib and another PD-L1 inhibitor durvalumab increased the frequency of ILD in EGFR mutation -positive NSCLC as compared to frequencies with either drug alone, although early data suggest encouraging clinical activity (R16-4467). Despite the fact that increased ILD frequency has not been reported when combining 1st or 2nd generation EGFR TKIs and immune checkpoint inhibitors, safety may still be a potential concern, thus careful safety measures have been implemented in this trial as further described in Sections: 1.4, 3.2, 5.2.6.1, and 8.7.

An ongoing phase I trial is assessing the combination of afatinib and pembrolizumab in patients with EGFR mutation-positive NSCLC with acquired resistance to erlotinib (NCT02364609). Information from this trial is taken into account for the determination of the recommended dose in the present trial (Appendix 10.9).

In the present trial, patients will receive afatinib and pembrolizumab at the approved recommended dose for the respective drugs. Twelve patients will be entered in the safety run in of the study and this data will be used to confirm the RP2D. Based on the observed safety profiles of both agents alone, it is expected that the combination can be initiated at 40 mg afatinib in combination with a fixed flat dose (200 mg every 3 weeks) of pembrolizumab. If excessive toxicities are observed at the 40 mg starting dose, the afatinib dose will be lowered to 30 mg as per the protocol, and twelve new patients will be entered in the safety run in to confirm the RP2D with afatinib 30 mg dose.

As mentioned above, patients will be monitored closely for adverse events and the dose of afatinib for individual patients will be interrupted or reduced, according to instructions provided in Table 4.1.4.1: 1.

Handling of the expected side effects is described in Section 4.2.3.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.2.6.1, adverse events of special interest (AESI).

During the trial, investigators are advised to manage treatment-related side-effects proactively. Suggested supportive care measures for the management of treatment related AEs and instructions for dose reductions for individual patients are provided in Section 4.1.4.

The patients will have frequent visits to ensure close monitoring of AEs. The safety of all patients, dose selection and benefit/risk assessment will be under constant surveillance by the

SMC (refer to Section 8.7) and by the Sponsor's Medical Monitor and Drug Safety Physician. The SMC will review the safety analysis based on BLRM to confirm the RP2D, and also the available safety data from all trials evaluating the combination of afatinib and pembrolizumab to confirm RP2D. The SMC will provide recommendations to either continue the trial without modification, or to stop recruitment, or to stop the trial at any of their meetings. The SMC may also provide recommendations to further minimize potential risks to patients, if required, e.g. regarding patient selection/ recruitment/dose adjustments, or request additional safety analysis. The SMC will operate under a Charter that will define membership, roles and responsibilities.

As part of the screening, patients are required to have a tumour tissue biopsy. In many cases this is standard clinical practice, and hence does not constitute an increased risk for the patients, but in case no fresh tissueis available this will be an additional procedure for some patients. As the results from the biopsy will provide more information which will assist clinical decisions for future patients, the benefit is assumed to outweigh the risks associated with the biopsy.

There will be regular and frequent examinations, including imaging every 9 weeks (63 ± 7 days) until PD/start of subsequent anti-cancer treatment.

Based on the disease under study, the inclusion of women of childbearing potential, using contraception as described in Section 4.2.2.3, is justified. To minimize the risk of unintentional exposure of an embryo or foetus to the investigational drug, women of childbearing potential must agree to the requirements for pregnancy testing and contraceptive methods as described in this protocol and patient information.

In summary, considering the high unmet medical need for new treatment options in patients with advanced or metastatic SCC of the lung who are progressing during or after prior platinum-based chemotherapy, the anti-tumour activity and the well-known safety profiles of monotherapy with afatinib and pembrolizumab, and the existing data suggesting that a combination of PD-1 blockade with EGFR TKIs is a promising therapeutic strategy, the benefit risk assessment for patients included into this trial is considered to be favourable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective is to assess the efficacy of afatinib in combination with pembrolizumab, as measured by objective response (OR) in patients with locally advanced or metastatic squamous NSCLC who progressed during or after first line platinum-based treatment.

The secondary objectives are to confirm the RP2D, assess the safety profile, and the secondary measures of clinical efficacy including disease control (DC), duration of objective response (DoR), progression-free survival (PFS), overall survival (OS), and tumour shrinkage.

2.1.2 Primary endpoint(s)

The primary endpoint for this study is Objective Response (OR), defined as best overall response of complete response (CR) or partial response (PR) from first drug intake until the earliest of disease progression, death, or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent.

All imaging related endpoints, including the primary endpoint will be investigator assessed primarily according to RECIST 1.1. Supportive summaries will also be produced with the supplemented immune-related RECIST (irRECIST) criteria. Refer to Sections 5.1, 7.3.1, 10.3, and 10.4 for further details.

2.1.3 Secondary endpoint(s)

Secondary endpoints in this trial consist of

- Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) from first drug intake until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent.
- Duration of objective response (DoR), defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with OR.
- Progression-free survival (PFS), defined as the time from first drug intake until disease progression or death from any cause, whichever occurs earlier.
- Overall survival (OS), defined as time from first drug intake until death from any cause.
- Tumour shrinkage (in millimeters), defined as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions.
- Recommended Phase II Dose (RP2D), defined by the SMC

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is an open-label, single arm phase II study assessing the tolerability and anti-tumour activity of afatinib when given in combination with a fixed dose of pembrolizumab in patients with squamous NSCLC, who progressed during or after first line platinum-based standard therapy and had no prior treatment with an immune checkpoint inhibitor or EGFR targeted therapy.

The trial consists of two parts:

Safety run in: After the first 12 patients have been treated for at least one full cycle, the SMC, (see Section 8.7) will assess the overall safety profile and confirm the RP2D (refer to Section 4.1.2).

The Bayesian Logistic Regression Model (BLRM) with overdose control will be fitted to binary toxicity outcomes to assess the risk for excessive toxicity. Please see Section 5.2.5.1 for the DLT definitions and Appendix 10.9 for details.

Based on the review of the clinical safety data together with the recommendations from the BLRM analysis, the SMC will decide if the starting dose of 40 mg of afatinib in combination with pembrolizumab should continue to be used for every new patient entering the study, or if it should be stopped and replaced by a dose of 30 mg afatinib. A stop of the 40 mg starting dose of afatinib is mandatory if this dose is considered too toxic according to the BLRM overdose criterion and all the available safety data. Hypothetical data scenarios have been performed for this purpose and are presented in Appendix 10.9.

The patients in the safety run in will continue in the trial during and after the SMC evaluation and in case the SMC confirms a dose of 40 mg daily afatinib is too toxic, their afatinib dose will be reduced to 30 mg. SMC will provide guidance whether to continue patient recruitment at the defined dose prior to the RP2D definition.

In case the 40 mg is too toxic, 12 more patients will be included in the safety run in and they will receive a starting dose of afatinib of 30 mg. After they have been treated for at least one full cycle, the SMC will assess the overall safety profile and confirm the RP2D as stated above. In case the RP2D is confirmed as 30 mg, the patients will continue on this dose. However, in case this is considered too toxic, the trial will be stopped (see Figure 3.1: 2).

The SMC met to assess the overall safety profile and overall response rates. Although the BLRM analysis of afatinib in combination with pembrolizumab satisfies overdose control criterion, the data presented does not support the continuation of the combination of afatinib and pembrolizumab in this clinical setting. The SMC recommended stopping the trial, as it was felt that the benefit risk was not favorable. The main part of the study will not open.

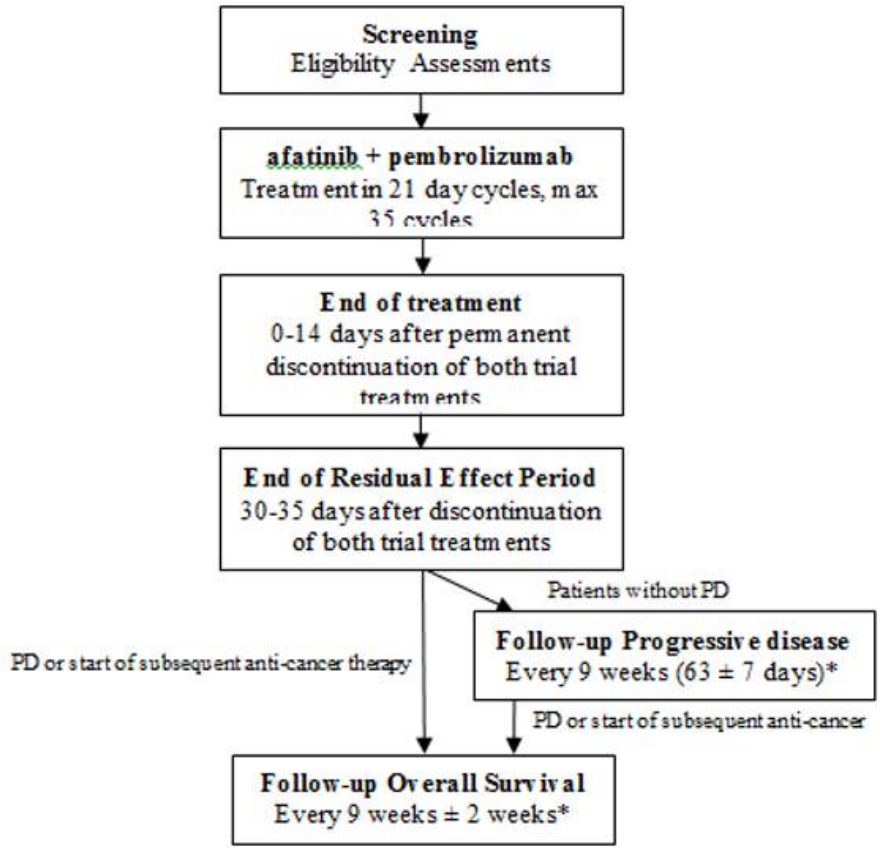
Main part: Once the RP2D has been established, this will be the starting dose of afatinib for future patients entered to the main part of the trial. In total, 38 patients will be included in the main part.

If the RP2D is defined as the original starting dose of afatinib (40 mg daily) in combination with pembrolizumab, the trial will include 12 patients from the safety run in and 38 patients from the main part, leading to 50 patients in total. However if the RP2D is defined as 30 mg

afatinib in combination with pembrolizumab, the trial will include 62 patients in total (12 patients at 40 mg and 50 patients at 30 mg).

In both the safety run in and the main part, there is an option for dose adjustment in the individual patients (see Section 4.1.4.1).

Detailed guidance on AE reporting, assessments of efficacy, and patient visits is given in Sections 5 and 6.



* The trial will be closed as defined in Section 8.6

Figure 3.1: 1 Trial Design

The trial design is applicable for both the safety run in and the main part (see Figure 3.1: 2). For SMC evaluation, please see Appendix 10.9.3. The end of trial is defined in Section 8.6.

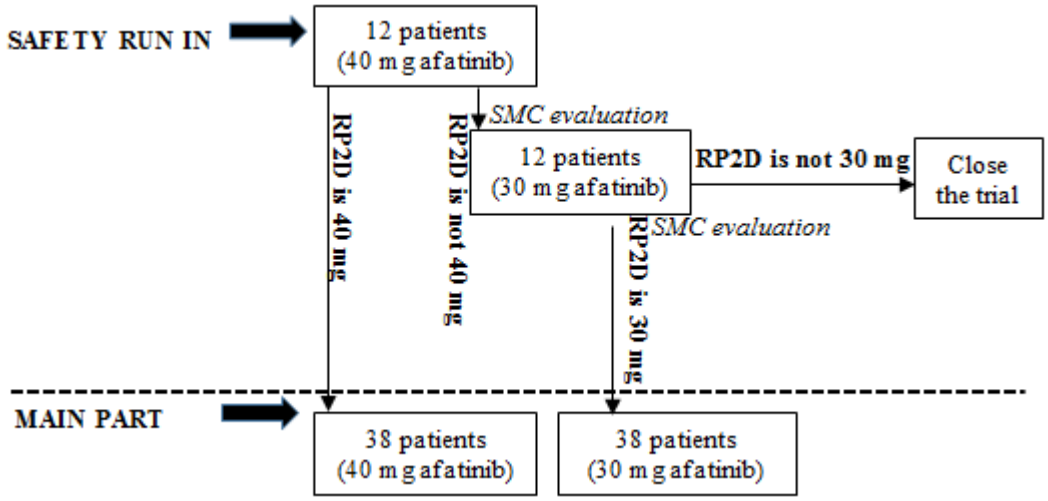


Figure 3.1: 2 Safety run in and main part

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This study is a single arm, non-randomised, open-label, phase II study. A single arm design is justified as the trial is exploratory in nature to generate safety and efficacy data of afatinib when given in combination with pembrolizumab in patients with locally advanced or metastatic SCC of the lung. Sections 1.3 and 1.4 give the rationale and benefit risk assessment of this single arm combination therapy study, over what has been observed with each of the single agents in previous studies. Section 1.3 also details the improvement in efficacy that is anticipated from the combination therapy to that observed in previous studies with each of the single agents (P15-06906, R15-6023).

The study will include a safety run in consisting of at least 12 patients, starting with afatinib 40 mg once daily plus pembrolizumab 200 mg once every 3 weeks. A Bayesian Logistic Regression Model (BLRM) with overdose control will be implemented to confirm the RP2D. In case the RP2D is not established with afatinib 40 mg, dose de-escalation to afatinib 30 mg will be implemented. Ongoing patients on afatinib 40 mg will have their dose reduced to 30 mg and any newly entered patients to the trial will start with afatinib 30 mg. In total, about 50 patients will be included at the RP2D. The dose selection will be determined based on the recommendation of the SMC, guided by the aforementioned modelling approach. The BLRM with overdose control is not only an efficient method for dose finding studies but also for dose confirmation due to its flexibility to react to unforeseen toxicity rates (R13-4802). The use of Bayesian models has also been proposed by the European Medicines Agency (EMA) guideline on small populations (R07-4845) and by the US Food and Drug Administration (FDA) (R13-4881).

A variety of cancers were demonstrated to express abundant levels of PD-L1 (R15-6033, R15-6038), which, via its interaction with the PD-1 receptor on tumour-specific T cells, plays a critical role in immune evasion by tumours (R15-6037). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer. Although higher responses were observed with pembrolizumab in patients with PD-L1 expression score ≥ 50%, the responses were also observed in patients with PD-L1 low (1-49%) or negative

(<1%) expression score. In addition, the significance of PD-L1 as a biomarker in predicting the effectiveness of checkpoint inhibition has been assessed with pembrolizumab monotherapy but not yet in combination with EGFR TKIs (R15-6023). Therefore no prospective patient selection based on PD-L1 expression score is planned; instead a retrospective assessment of PD-L1 expression score will be performed and its impact evaluated. Exploratory subgroup analyses for efficacy endpoints based on PD-L1 expression status will be performed.

Pembrolizumab and afatinib trial treatments as combination may be continued for up to 35 cycles, which is the approved treatment duration for pembrolizumab monotherapy. In case of early discontinuation of one agent, the other agent may be continued as monotherapy for up to 35 cycles (including cycles with the combination treatment). After EOT, further therapy will be decided by the investigator including either continuation of afatinib (using commercial product), or alternative therapy, or best supportive care.

The primary endpoint of the study is Objective Response (OR), which is a well-accepted endpoint for a single arm phase II study. A response rate in excess of historical data in this population with demonstrated durability of such response can serve as a reasonable surrogate for clinical benefit in pre-treated locally advanced or metastatic squamous NSCLC.

3.3 SELECTION OF TRIAL POPULATION

This trial will be conducted at approximately 25 centres in about 6 countries. If a centre is unable to recruit patients, additional centres may be recruited and centres may be closed. Each centre is expected to recruit on average of 2-3 patients.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Sites will be notified about screening completion and will then not be allowed to screen additional patients for this trial. When the required number of patients has entered the study, patients who have already been screened for the trial are allowed to continue and be entered in case they meet all eligibility criteria.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site file (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

This study will include patients with locally advanced or metastatic squamous cell carcinoma of the lung. Patients must have progressed during or after standard platinum-based chemotherapy, without prior treatment with any checkpoint inhibitor or EGFR targeted therapy.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Pathologically confirmed diagnosis of NSCLC considered to be of squamous histology, including mixed histology, in the opinion of the investigator.

2. Locally advanced (stage IIIb) or metastatic (stage IV) NSCLC not considered eligible for curative therapy.
3. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV SCC of the lung. This includes patients relapsing within 6 months of completing (neo) adjuvant/curative-intent chemotherapy or definitive chemoradiotherapy. Patients should be eligible to receive second line therapy in the opinion of the investigator.
4. At least one target lesion (outside the brain) that can be accurately measured per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. In patients who only have one target lesion and a biopsy of the lesion is required; the baseline imaging must be performed at least two weeks after the biopsy.
5. Availability and willingness to provide a fresh tumour tissue sample obtained after relapse or progression on or after prior therapy. In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen may be submitted.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Adequate organ function defined as all of the following (all screening labs should be performed within 10 days prior to treatment initiation):

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L.
Platelets	≥75 x 10^9/L.
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L.[a]
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl)	≤ 1.5 x ULN **OR** ≥50 mL/min for patients with creatinine levels >1.5x ULN.
Hepatic	
Total bilirubin	≤1.5 times the upper limit of normal (ULN)
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases.
Coagulation	
• International Normalised Ratio (INR) or Prothrombin Time (PT)	• ≤1.5xULN unless patient is receiving anticoagulant therapy as long as PT is within therapeutic range of intended use of anticoagulants.
• Activated Partial Thromboplastin Time (aPTT)	• ≤1.5xULN unless patient is receiving anticoagulant therapy as long as aPTT is within therapeutic range of intended use of anticoagulants.
[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. [b] Creatinine clearance should be calculated per institutional standard.	

8. Recovery from major surgery or any previous anti-cancer or radiation therapy-related toxicity to ≤ CTCAE Grade 1 at C1_V1 (except for alopecia; stable sensory neuropathy must be ≤ CTCAE Grade 2).
9. At least 18 years of age or over the legal age of consent in countries where that is greater than 18 years at screening.

10. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
11. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 120 days after the last dose of pembrolizumab treatment and 2 weeks after last afatinib treatment, respectively, as listed in the protocol. A list of contraception methods meeting these criteria is provided in the patient information. For further details refer to Section 4.2.2.3. Note: Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.

3.3.3 Exclusion criteria

1. Prior therapy with any immune checkpoint inhibitor; however, prior (neo) adjuvant checkpoint inhibitor therapy is allowed if completed at least 12 months before relapse.
2. Prior therapy with EGFR inhibiting drugs; however, prior EGFR-targeted (neo) adjuvant therapy is allowed if completed at least 12 months before relapse.
3. Treatment with prior chemotherapy, non-EGFR targeted therapy, or anti-cancer hormonal treatment within 2 weeks prior to the first dose of trial treatment.
4. Current or previous treatment with experimental therapy or use of an investigational device within 30 days prior to the first dose of trial treatment.
5. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the first dose of trial treatment.
6. Received a live vaccine within 30 days prior to the first dose of trial treatment. Seasonal flu vaccines that do not contain live virus are permitted.
7. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids is allowed.
8. Any history of or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the trial or interfere with the evaluation of the efficacy and safety of the test drugs.
9. Radiotherapy within 4 weeks prior to start of treatment except as follows:
    - Palliative radiotherapy to regions other than the chest is allowed up to 2 weeks prior to start of treatment;

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- Single dose palliative radiotherapy for symptomatic metastasis within 2 weeks prior to start of treatment may be allowed but must be agreed with the sponsor.

10. Major surgery (according to the investigator's assessment) performed within 4 weeks prior to start of treatment or planned during the projected course of the study.
11. Requirement or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
12. Known history of hypersensitivity to afatinib or any of its excipients.
13. Known history of hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
14. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

    Note: Patients with previously treated brain metastases may participate provided they are radiologically stable i.e. without evidence of progression for at least four weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroids treatment for at least 14 days prior to first dose of study treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
15. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
16. History of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids or current ILD/pneumonitis.
17. Any history or presence of uncontrolled gastrointestinal disorders that could affect the intake and/or absorption of the study drug (e.g. nausea, vomiting, Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption) in the opinion of the investigator.
18. Active infectious disease requiring systemic therapy or which puts the patient at increased risk in the opinion of the investigator.
19. Previous or concomitant malignancies at other sites than the lung, except:
    - Effectively treated non-melanoma skin cancers;
    - Effectively treated carcinoma in situ of the cervix;
    - Effectively treated ductal carcinoma in situ;
    - Other effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured.
20. Known human immunodeficiency virus (HIV) (HIV 1/2 antibodies), hepatitis B (e.g. HBsAg reactive) or known active hepatitis C infection.
21. History of active TB (Bacillus Tuberculosis).
22. History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure New York Heart Association (NYHA) classification of ≥3,

unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the investigator. Myocardial infarction within 6 months prior to start of treatment.

23. Psychiatric, substance abuse disorders, or chronic alcohol abuse or any condition that in the investigator's opinion would interfere with cooperation with the requirements of the trial.
24. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation in the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
25. Is pregnant or breastfeeding, expecting to conceive or father children within the projected duration of the trial or do not agree to submit to the pregnancy testing required by this protocol.

3.3.4 Withdrawal of patients from therapy or assessments

With the early termination of the study, there is no follow-up of patients who completed the trial.

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the entered patients in the trial: if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial entry, as well as the explanation of the consequences of withdrawal.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and eCRF.

3.3.4.1 Withdrawal from trial treatment

With the early termination of the study there will be no follow-up for disease progression or overall survival after a patient is withdrawn from trial treatment.

An individual patient is to be withdrawn from trial treatment if the patient:

- Wants to withdraw from trial treatment, without the need to justify the decision.
- Is diagnosed with Interstitial Lung Disease (ILD) / pneumonitis
  - afatinib: any grade
  - pembrolizumab: grade >2 or recurrent grade 2
- Is required to stop treatment due to adverse events as described in Section 4.2.3 and 4.1.4.
- Can no longer be treated with trial medication due to pregnancy or for other medical reasons (such as surgery, concomitant diagnoses, adverse events, or prohibited concomitant therapies (refer to Section 4.2.2).

- Has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or not able to stick to the trial requirements in the future.
- Has a significant deviation from the protocol procedures or eligibility criteria. The decision to continue or withdraw treatment will be made by the sponsor in agreement with the investigator.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flowchart and Section 6.2.3. FU/PD will be performed until confirmed PD, and FU/OS will be performed until the end of trial.

An individual patient will complete trial treatment if the patient:

- Has radiological (or clinical) documentation of progressive disease on the current treatment (see Section 5.1.2).
- Has completed the maximum 35 cycles of study treatment.

Given the patient's agreement, the patient will undergo the procedures and follow-up as outlined in the Flowchart and Section 6.2.3. FU/PD will be performed until confirmed PD, and FU/OS will be performed until the end of trial.

For all patients the reason for discontinuation of trial treatment (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow-up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow-up after withdrawal from trial treatment, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Eligible patients will receive a combination of afatinib and pembrolizumab.

4.1.1 Identity of the investigational medicinal products

Table 4.1.1: 1 Afatinib (investigational medicinal product)

Substance (INN): Brand name:	Afatinib GIOTRIF®/ GILOTRIF®
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	40 mg tablet, 30 mg tablet, 20 mg tablet
Posology	Once daily
Route of administration:	Oral

Table 4.1.1: 2 Pembrolizumab (investigational medicinal product)

Substance (INN): Brand name:	Pembrolizumab
Pharmaceutical formulation:	Solution for infusion
Source:	
Unit strength:	Solution for infusion: 100 mg/4mL
Posology:	Infusion, once every 3 weeks
Route of administration:	Intravenous

4.1.2 Selection of doses in the trial

In this trial, afatinib will be given at the approved single-agent starting dose i.e. 40 mg once daily, in combination with pembrolizumab at the approved single-agent fixed dose of 200 mg every 3 weeks. Based on available data from an ongoing phase I trial in EGFR mutant NSCLC (NCT02364609), a starting dose of afatinib at 40 mg once daily in combination with pembrolizumab is considered feasible. The daily dose of afatinib may be adjusted following

careful monitoring of patients' side effects, as depicted in Table 4.1.4.1: 1, with dose reduction to 30 mg or 20 mg for patients experiencing AEs (see Section 4.1.4).

The SMC will review the safety analysis based on BLRM to confirm the RP2D, which will be the starting dose of afatinib given in combination with pembrolizumab for any future patients entered to the trial. The starting dose of afatinib can be reduced to 30 mg based on the SMC recommendation.

4.1.3 Method of assigning patients to treatment groups

All eligible patients will receive afatinib in combination with pembrolizumab. The assignment of an afatinib medication number and a pembrolizumab medication number will occur via Interactive Response Technology (IRT). Patient numbers will be provided by the IRT system once the patient is registered in the system. Re-screening is allowed.

4.1.4 Drug assignment and administration of doses for each patient

Patients will receive continuous treatment from C1_V1 until progression or until other criteria for stopping medication are met (see Section 3.3.4.1). The SMC review of the safety analysis based on BLRM recommendations and additional safety data will confirm the RP2D (see Section 4.1.2). Patients will be monitored closely for adverse events and dose modifications may apply, according to instructions provided in Table 4.1.4.1: 1 and Table 4.1.4.2.1: 1 below. In case of treatment related Adverse Events that cannot exclusively be attributed to one compound, the instructions for dose modification of both compounds should be taken into consideration. The starting dose of afatinib can be reduced to 30 mg based on the SMC recommendation.

Stopping rules and retreatment criteria for each compound should be considered separately. In case afatinib has to be (temporarily) interrupted, pembrolizumab treatment may continue at the investigator's discretion.

After first documentation of PD and if the patient is clinically stable, the patient may continue study treatment at the physician discretion if it is felt patient is still deriving a benefit from treatment until confirmed PD (see Table 5.1.2: 1). This clinical judgment decision by the site should be based on the patients' overall clinical condition, including performance status, clinical symptoms, and laboratory data. Tumour assessment should be repeated at least 4 weeks later in order to confirm PD by irRECIST. In case treatment is paused and disease progression is not confirmed on subsequent imaging, study treatment may be resumed.

Pembrolizumab and afatinib study medication will not be continued after the development of confirmed PD (see Section 5.1).

Refer to Section 4.2.3 for instructions on the management of treatment related AEs.

Dosing interruptions are permitted in 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). Patients should be placed back on study therapy within 14 days of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the patient's study record.

4.1.4.1 Afatinib treatment

Patients will take a single oral dose of afatinib each day starting at a dose of 40 mg, continuously, until the development of progressive disease or until other criteria for stopping medication are met. Dose reductions of afatinib can occur (see Table 4.1.4.1: 1). Once the SMC has confirmed the RP2D, this will be the starting dose of afatinib.

On day 1 of each treatment cycle, patients will be dispensed sufficient afatinib for the treatment cycle. Any medication remaining from the previous treatment cycle should be collected. If a dose reduction is necessary during a treatment cycle, any remaining medication from the higher dose should be collected from the patient and the new dose dispensed.

The afatinib tablet should be taken once daily (qd) at approximately the same time of the day, with a glass of water, and food should not be consumed for at least three hours before and at least one hour after taking the afatinib tablet. Missed doses of afatinib can be made up for during the same day, if taken within 8 hours of the regularly scheduled time. Otherwise, the dose should be skipped and patients should take the next scheduled dose at the usual time. Afatinib tablets should not be taken more than once a day and patients with emesis should not take a replacement dose. On the visit dates of Cycle 2 and Cycle 3, respectively, the patient should not take the dose at home before visiting the site, as the afatinib medication is taken at the study site shortly after the PK sampling and before start of pembrolizumab infusion (see Section 10.1).

If dosing of whole tablets is not possible, afatinib tablets can also be dispersed in approximately 100 ml of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped in the water, without crushing it, and occasionally stirred for up to 15 min until the tablet is broken up into very small particles. The dispersion should be drunk immediately. The glass should be rinsed with approximately 100 ml of water which should also be drunk. The dispersion can also be administered through a naso-gastric tube.

Patients will be monitored closely for adverse events and the dose of afatinib must be interrupted or reduced, according to instructions provided in Table 4.1.4.1: 1 below. Once the dose has been reduced, it may not be increased later.

Table 4.1.4.1: 1 Afatinib dose reduction scheme

AE type and CTCAE Grade	Action	Dose reduction scheme
Events related to afatinib: • Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration • Reduced renal function due to dehydration (i.e. pre-renal failure) secondary to diarrhoea	Pause afatinib until patient has recovered to CTCAE Grade ≤1 or baseline level[1] Resume afatinib at reduced dose according to schedule opposite. If patient has not recovered to CTCAE Grade ≤1 or baseline[1] within 14 days afatinib	If patient was receiving 40 mg, resume treatment at a dose of 30 mg If patient was receiving 30 mg, resume treatment at a dose of 20 mg If patient was receiving 20 mg, discontinue afatinib.

AE type and CTCAE Grade	Action	Dose reduction scheme
to ≥ Grade 2 as measured by serum creatinine, proteinuria, or decrease in glomerular filtration rate of more than 50% from baseline • Any drug related AE Grade ≥3	study treatment must be permanently discontinued[2]	
Acute onset and/or unexplained worsening of pulmonary systems (dyspnoea, cough, fever)	Pause afatinib while clinical assessment to exclude ILD is completed	If ILD/pneumonitis is confirmed, discontinue afatinib If ILD/pneumonitis is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs unless there is another diagnosis If AEs are not related, resume afatinib at current dose. If AEs are drug related, follow directions in row above For pembrolizumab: refer to Table 4.1.4.2.1: 1

1. Baseline is defined as the CTCAE Grade prior to the start of treatment.
2. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.

In the event of a treatment pause, subsequent visits should not be delayed.

In the event of any unrelated adverse events, the investigator may choose to interrupt the medication for up to 14 days, but no dose reduction should occur. If the medication is interrupted for more than 14 days, the decision to continue with afatinib will be made by the BI medical monitor in agreement with the investigator.

In case the criteria for discontinuing afatinib are met, treatment with pembrolizumab can continue until a maximum of 35 cycles, see Section 4.1.4.2.

4.1.4.2 Pembrolizumab treatment

Pembrolizumab will be administered on Day 1 of each 21 day treatment cycle after all study procedures and assessments have been completed. Pembrolizumab will be administered as a dose of 200 mg using a 30-minute i.v. infusion. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted i.e., infusion time is 30 minutes (-5 min/+10 min).

Pembrolizumab and afatinib trial treatment may be continued, as combination or mono therapy, for a maximum period of 35 cycles (about two years) after which study medication(s) must be discontinued / completed. Further therapy will be decided by the investigator and may include: continuation of afatinib using commercial product according to current SPC/PI, or alternative therapy, or best supportive care.

4.1.4.2.1 Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.1.4.2.1: 1.

See Section 4.2.3 for supportive care guidelines, including use of corticosteroids.

Table 4.1.4.2.1: 1 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAE v4.03)**	**Action taken to pembrolizumab[1]**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.03)	Action taken to pembrolizumab[1]	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
				• Add prophylactic antibiotics for opportunistic infections
Diarrhoea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • For afatinib: refer to Table 4.1.4.1: 1	• Monitor patients for signs and symptoms of enterocolitis (i.e. diarrhoea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus) • Patients with ≥ Grade 2 diarrhoea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Patients with diarrhoea/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 i.v. infusion
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin[1]	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.03)	Action taken to pembrolizumab[1]	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycaemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of ß-cell failure	Withhold	• Initiate insulin replacement therapy for patients with T1DM • Administer anti-hyperglycemic in patients withhyperglycemia	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[2]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue[2]		
Hypothyroidism	Grade 2 to 4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis or renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other Immune-Related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.03)	Action taken to pembrolizumab[1]	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Notes:
[1] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
[2] For patients with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

In case the criteria for discontinuing pembrolizumab are met, treatment with afatinib can continue, see Section 4.1.4.

4.1.4.2.2 Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the patient's study record.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

Patients will be handed out afatinib trial medication for the upcoming treatment cycle during the planned and/or regular visit on day 1 of each treatment cycle. Medication not used in the previous treatment cycle and empty bottles will be collected.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

Details on storage conditions for pembrolizumab are provided in the Pharmacy Manual.

4.1.8 Drug accountability

The investigator or delegate (e.g. pharmacist or investigational drug storage manager) will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee.
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site.
- Approval/notification of the regulatory authority, e.g. competent authority.
- Availability of the curriculum vitae of the Principal Investigator.
- Availability of a signed and dated clinical trial protocol.
- Availability of the proof of a medical license for the Principal Investigator.
- For US only: Availability of FDA Form 1572.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or delegate must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator or delegate will maintain records that document adequately that the patients were provided the doses specified by the clinical trial protocol and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or delegate must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed for afatinib.

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. In cases of suspected overdose, afatinib should be withheld and supportive care initiated. If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage. Rescue medications to reverse the actions of pembrolizumab are not available. Potential adverse events should be treated symptomatically and must be recorded.

Common adverse events of treatment with afatinib with specified management recommendations and/or requirements include diarrhoea, stomatitis/mucositis, and rash/acne. For pembrolizumab, related adverse events are those with potential immunologic etiology. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described in Section 4.2.3.

For pembrolizumab, patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 4.1.4.2.1 (Table 4.1.4.2.1: 1). Where appropriate, these guidelines include the use of oral or i.v. treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4.1.4.2.1: 1 in Section 4.1.4.2.1 for guidelines regarding dose modification and supportive care.

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

4.2.1.1 Concomitant medications

Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

After study enrolment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area cannot be used for further tumour response assessment. During palliative radiotherapy, study treatment should

be delayed and may be resumed once the patient has recovered from any radiation associated toxicity. If medication is interrupted for more than 14 days, the decision to continue will be made by the sponsor in agreement with the investigator.

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies and nutritional supplements must be recorded in the eCRF during the screening and treatment period, starting from the date of signature of informed consent, and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patients are prohibited from receiving the following therapies or vaccination during the trial treatment:

- Any other investigational agents apart from the study medication.
- Anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment (with the exception of megestrol acetate and use of anti-androgens and/or gonadorelin analogues for treatment of prostate cancer), biological therapy, or radiotherapy (other than described in Section 4.2.1.1). The use of megestrol acetate to improve appetite and to increase weight in cancer-associated anorexia is allowed.
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with the sponsor. The patient must have clear measurable disease outside the radiated field.
- Immunotherapy not specified in this protocol.
- 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.
    - Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.
    - However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology or to treat adverse reactions to afatinib. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
    - Inhaled steroids are allowed for management of asthma.
    - Steroid pre-medications for contrast CTs are permissible if needed.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be withdrawn from the trial treatment. Patients may receive other medications that the investigator deems to be medically necessary. The final decision on any supportive therapy or vaccination rests with the

investigator and/or the patient's primary physician. However, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the sponsor and the patient.

The Exclusion Criteria describe other medications that are prohibited in this trial.

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

The following guidance is applicable for afatinib:

- Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib with strong P-gp modulators. For a list of potent P-gp inhibitors and inducers see Appendix 10.8.
- In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib around one week prior to the surgery, and to restart treatment after wound healing. If afatinib is interrupted for more than 14 days, the decision to continue will be made by the BI Medical Monitor in agreement with the investigator.

4.2.2.2 Restrictions on diet and life style

Patients should be advised to avoid any foods known to aggravate diarrhoea.

To prevent skin related adverse events it is recommended to avoid intense irradiation with UV light and harsh detergents, see also Section 4.2.3.

Food should not be consumed for at least three hours before and at least one hour after taking the afatinib tablet.

On the visit dates of Cycle 2 and Cycle 3, respectively, the patient should not take the dose at home before visiting the site, as the afatinib medication is taken at the study site shortly after the PK sampling and before start of pembrolizumab infusion (see Section 10.1).

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

Women who are not of childbearing potential due to being postmenopausal (i.e. 12 months with no menses without alternative medical cause, predefined hormonal level according to local regulation) and patients (male or female) who are permanently sterilised (bilateral oophorectomy or hysterectomy confirmed with medical records of the actual procedure or confirmed by an ultrasound, bilateral salpingectomy, vasectomy) do not need to use contraception to be eligible for the trial.

All other patients (male or female) are considered to have childbearing potential and must use adequate contraception throughout the trial (from screening until 120 days after the last dose of pembrolizumab treatment and 2 weeks after last afatinib treatment).

Adequate contraception is defined per ICH M3 (R2) as highly effective or acceptable methods. Highly effective methods of birth control which should be used by women of childbearing potential are those, which alone or in combination, result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, and must be in accordance with local regulations where applicable.

Based on the recommendations of the European Union Heads of Medicines Agency related to contraception and pregnancy testing in clinical trials (CTFG, 2014), the following contraception methods can achieve a failure rate of less than 1% per year when used consistently and correctly:

1. Use of hormonal methods of contraception associated with inhibition of ovulation
    a. Combined (estrogen and progestogen containing) hormonal contraception:
        - Oral
        - Intravaginal
        - Transdermal
    b. Progestogen-only hormonal contraception:
        - Oral
        - Injectable
        - Implantable
2. Placement of intrauterine device or intrauterine system.
3. Bilateral tubal occlusion.
4. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
5. Complete sexual abstinence.

The list of acceptable contraception methods is also provided in the patient information.

Women who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy must be reported following procedures detailed in Section 5.2.6.2.

4.2.3 Management of side effects

Management of treatment-related side-effects should be proactive and should be started as early as possible after onset of symptoms. Patients should be advised to report AEs promptly so that appropriate treatment can be initiated.

Suggested supportive care measures for the management of adverse events due to treatment with EGFR targeting agents or with potential immunologic etiology are outlined below.

When managing side effects, consider both afatinib and pembrolizumab instructions as provided below.

Patients 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, the measures for pembrolizumab adverse reactions 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 cycles 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).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. See also Table 4.1.4.2.1: 1 for more information about toxicity management and dose modification guidelines for irAEs associated with pembrolizumab.

Refer to the pembrolizumab IB (c16013985) for more information.

4.2.3.1 Management of dermatological AEs following treatment with afatinib

Dermatologic AEs observed with afatinib include rash, dermatitis acneiform, and dry skin (xerosis)/hyperkeratosis. General recommendations for prophylaxis are summarised in Table 4.2.3.1: 1 and grade-specific treatment recommendations are summarised in Table 4.2.3.1: 2 (adapted from R11-0826).

Specific interventions should be reassessed at least after 2 weeks or at any worsening of symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered.

Table 4.2.3.1:1 General recommendations for prophylaxis of dermatological AEs while receiving afatinib

Table 4.2.3.1: 1 General recommendation for prophylaxis of dermatological AEs while receiving afatinibPersonal hygiene	Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water. Use of very mild shampoos for hair wash. Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. Fine cotton clothes should be worn instead of synthetic material. Shaving has to be done very carefully. Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections.
Sun protection	Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high Sun Protection Factor (SPF) (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended. Patients should be encouraged to consequently stay out of the sun. Protective clothing for sun protection and wearing a hat should be recommended.
Moisturiser treatment	It is important to moisturise the skin as soon as anti-EGFR therapy is started. Hypoallergenic moisturising creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications.
Prevention of paronychia	Patients should keep their hands dry and out of water if ever possible. They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 4.2.3.1: 2 Grade specific treatment recommendations of skin reactions to afatinib

Intensity (CTCAE Grading)	**Description**	**Specific intervention**
ACNEIFORM RASH		
Mild (Grade 1)	Papules and/or pustules covering <10% Body Surface Area (BSA), which may or may not be associated with symptoms of pruritus or tenderness.	Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1%. Isolated scattered lesion: cream preferred; Multiple scattered areas: lotion preferred.
Moderate (Grade 2)	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL.	Topical treatment as for Grade 1 plus short term topical steroids, e.g. prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. doxycycline 100 mg (b.i.d.) or minocycline hydrochloride 100 mg b.i.d.
Severe (Grade 3)	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated.	Topical and systemic treatment as for Grade 2. Consider referral to dermatologist. Consider systemic steroids.
Life threatening (Grade 4)	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with i.v. antibiotics indicated; life threatening consequences.	See Grade 3 Systemic antibiotics and steroids are recommended.
PRURITUS		
Mild (Grade 1)	Mild or localised; topical intervention indicated.	Topical polidocanol cream. Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine).
Moderate (Grade 2)	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL.	See Grade 1 plus oral antihistamines; Consider topical steroids, e.g. topical hydrocortisone.

Intensity (CTCAE Grading)	**Description**	**Specific intervention**
Severe (Grade 3)	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated.	See Grade 2
XEROSIS (DRY SKIN)/HYPERKERATOSIS		
Hyperkeratotic skin rash was previously observed in patients treated with afatinib. It is characterised by dryness, feeling of "thickening of the skin" and appearance of desquamating hyperkeratotic plaques on palms and soles, on extensor surfaces of knuckles of fingers and toes and less frequently on elbows or knees.		
Mild (Grade 1)	Covering <10% BSA and no associated erythema or pruritus.	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream). Over-the-counter moisturising cream or ointment to face b.i.d. AND Ammonium lactate 12% cream to body OR Urea 10-20% cream b.i.d.

Intensity (CTCAE Grading)	**Description**	**Specific intervention**
Moderate (Grade 2)	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL.	Over-the-counter moisturising cream or ointment to face b.i.d. AND Ammonium lactate 12% cream OR Salicylic acid 3% cream to body b.i.d. OR Urea 10-20% cream b.i.d. AND Topical steroid* to eczematous areas b.i.d.
Severe (Grade 3)	Covering >30% BSA and associated with pruritus; limiting self-care ADL.	Over-the-counter moisturising cream or ointment to face b.i.d. AND Ammonium lactate 12% cream OR Salicylic acid 3% cream to body b.i.d. AND Topical steroid* to eczematous areas b.i.d.
*Moderate/low strength topical steroids e.g. triamcinolone acetonide 0.025% cream, desonide 0.05% cream or lotion, aclometasone 0.05% cream, fluticasone propionate 0.05% cream or lotion.		
FISSURES		
NA	Asymptomatic	Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths). Topical application of aqueous silver nitrate solutions to fissures.
NA	Symptomatic, not interfering with ADL	As above and also consider oral antibiotics.
NA	Symptomatic, interfering with ADL	As above and also consider oral antibiotics.

If a Grade 2 AE as described above persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator has the option to pause treatment and perform a dose reduction in accordance with Section 4.1.4.1.

4.2.3.2 Management of keratitis following treatment with afatinib

Keratitis has been reported following treatment with currently approved EGFR targeting agents. Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis,

ulcerative keratitis, or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

4.2.3.3 Management of diarrhoea and hydration status following treatment with afatinib and pembrolizumab

Following treatment with afatinib, diarrhoea occurs at a high frequency and although usually mild to moderate, it may lead to dehydration and require treatment modification or discontinuation, so early management is essential (Table 4.2.3.3: 1). At the time of initiation of trial treatment patients should be given a supply of anti-diarrhoeal medication such as loperamide or a prescription hereof to keep with them at all times or access to anti-diarrhoeal medication should be confirmed; and patients should be counselled on the appropriate use.

Following treatment with pembrolizumab, patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). Further instructions are provided in Table 4.1.4.2.1: 1.

Table 4.2.3.3: 1 Management guidelines for diarrhoea for patients taking the combination of afatinib and pembrolizumab

Intensity (CTCAE Grading) and Description	**Intervention concerning afatinib treatment**	**Intervention concerning pembrolizumab treatment**	**Specific intervention**
Mild (Grade 1) • Increase of < 4 stools per day over baseline • Mild increase in ostomy output compared with baseline	Continue same dose	Continue same dose	• Stop laxatives and advise patient to drink at least 8-10 glasses of water or clear fluids per day • Anti-diarrhoeal medication such as loperamide 4 mg (2 tablets) to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (Grade 2) • Increase of 4-6 stools per day over baseline • i.v. fluids indicated < 24 hours • Moderate increase in ostomy output compared with baseline	Continue same dose unless Grade 2 diarrhoea continues for ≥ 2 days (48 hours) or is intolerable despite starting anti-diarrhoeal treatment, in which case treatment must be interrupted until recovered to ≤ Grade 1 followed by dose reduction	Withhold	• Continue anti-diarrhoeal medication. • Assess for dehydration and electrolyte imbalance. Consider i.v. fluids and electrolyte replacement. • In case Grade 2 diarrhoea continues despite interruption of afatinib for ≥ 2 days (48 hours), administer oral corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Monitor patients for signs and symptoms of enterocolitis and of bowel perforation • In case colitis is suspected, consider GI consultation and performing endoscopy. For more details about colitis, see Table 4.1.4.2.1: 1
Severe (Grade 3) • Increase of ≥7 stools per day over baseline • Incontinence • Hospitalization indicated • Severe increase in ostomy output compared with baseline • Limiting self-care Activities of Daily Living (ADL)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	Withhold	• See Grade 2, plus: • An infectious process should be ruled out with stool cultures • Aggressive i.v. fluid replacement ≥ 24 hours • Hospitalization to monitor progress • Consider prophylactic antibiotics if patient is also neutropenic or febrile • Start i.v. steroid treatment followed by high dose oral steroids
Life threatening (Grade 4) • Life-threatening consequences; urgent intervention indicated	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	Permanently discontinue	• See Grade 3

* If despite optimal supportive care and treatment interruption, diarrhoea does not resolve to CTCAE Grade ≤ 1 within 14 days, treatment with afatinib must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.

4.2.3.4 Management of interstitial lung disease/pneumonitis following treatment with afatinib/pembrolizumab

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude interstitial lung disease (ILD)/pneumonitis. Afatinib and pembrolizumab should be interrupted pending investigation of these symptoms. If ILD/pneumonitis is diagnosed, both study drugs must be permanently discontinued and appropriate treatment instituted as necessary (see below).

- 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 or recurrent Grade 2**, 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.

If ILD is ruled out as a cause of symptoms, assess causality and apply the follow the instructions provided in Table 4.1.4.1: 1.

4.2.3.5 Management of type 1 diabetes mellitus following treatment with pembrolizumab

Provided that: new onset, including diabetic ketoacidosis (DKA) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

For type I diabetes mellitus 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.

4.2.3.6 Management of hypophysitis following treatment with pembrolizumab

- 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 i.v. 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.

4.2.3.7 Management of hyperthyroidism or hypothyroidism following treatment with pembrolizumab

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of i.v. 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.

4.2.3.8 Management of hepatic events following treatment with pembrolizumab

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with i.v. 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.

4.2.3.9 Management of renal failure or nephritis following treatment with pembrolizumab

- 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 for at least 4 weeks.

4.2.3.10 Management of infusion reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.2.3.10: 1.

Table 4.2.3.10: 1 Pembrolizumab infusion reaction dose modification and 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 patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: i.v. fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient 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 patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of analgesic).
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: Epinephrine** i.v. fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately Patient is permanently discontinued from further trial treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.03 at http://ctep.cancer.gov		

4.3 TREATMENT COMPLIANCE

Patients should take the first dose of afatinib treatment at the trial site and subsequent doses will be taken at home. On day 8, the site personnel should discuss treatment compliance with the patient, to ensure that the medication is taken correctly. Patients are requested to bring all remaining trial medication including empty package material with them when attending visits for a compliance check, i.e. at the end of each 21 day cycle.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be recorded at the investigator site and verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented in the site file and explained. If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance. If the patient is eligible for further treatment, a new study medication kit must be dispensed.

The investigator and/or the sponsor can withdraw a patient from further study treatment in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results for this patient unacceptable.

Pembrolizumab will be administered at the trial site under the supervision of the investigator. In the event that the patient does not receive the full dose of pembrolizumab this should be documented and a reason given.

Drug holidays, if previously agreed with the investigator and sponsor, e.g. vacation, will not be considered non-compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Tumour imaging

With the early termination of the study, tumour assessment is per local standard and the timing and methods of imaging should follow local practice until PD, start of subsequent anti-cancer treatment or withdrawal from study treatment.

Imaging will be performed as indicated in the Flowchart and Appendix 10.3. The process for image collection and storage can be found in the Imaging Manual in case of a retrospective independent review. Tumour imaging should be performed by computed tomography (CT) (preferred). Magnetic resonance imaging (MRI) should only be used when CT is contraindicated or for imaging in the brain, but the same imaging technique should be used in a patient throughout the trial. CT scan is the more commonly used modality and is preferred for the majority of patients. Imaging should include the chest, abdomen, and pelvis, and, if clinically indicated, imaging of any other known or suspected sites of disease using an appropriate method according to clinical practice at the site. Local site study team reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine patient eligibility.

Copies of tumour images used for the assessment of the primary endpoint should be stored at each investigational site. including images performed to evaluate potential ILD. If a retrospective independent review is required then a copy of the tumour images will be submitted to the central image vendor. In case of a retrospective independent review, the process for image collection and storage will be described in the Imaging Manual.

Baseline imaging
All baseline evaluations must be performed as close as possible and within 28 days before first drug intake. In patients who only have one target lesion and a biopsy of the lesion is required; the baseline imaging must be performed at least two weeks after the biopsy. Pre-trial imaging, performed as part of routine clinical practice, can be used as the baseline imaging given that the imaging results are of diagnostic quality and within the allowed time window. Otherwise, the scan must be repeated at screening. In case there are multiple screening scans, the latest evaluable scan should be used for the trial. The site study team must review screening images to confirm the patient has measurable disease per RECIST 1.1.

Imaging during trial
The examinations should be performed every 9 weeks (63 ± 7 days) until confirmed PD or start of subsequent anti-cancer therapy. In case of a delay, interruption, or discontinuation of study medication or visits, imaging must continue to follow the original schedule. After PD or response per RECIST, repeat imaging for confirmation is required.Confirmatory imaging is repeated at ≥ 4 weeks later to confirm PD; for SD, PR, or CR the regularly scheduled imaging is assessed (or as early as 4 weeks later).

Continue to perform imaging until whichever of the following occurs first:

- Initial site-assessed PD is verified by repeat imaging
- Start of subsequent anti-cancer treatment
- Withdrawal of consent

- Death
- The end of the study

5.1.2 Imaging review

With the early termination of the study, tumour response and progression are per local practice and guidelines and do not have to follow RECIST.

Response and progression will be evaluated primarily according to Response Evaluation Criteria in Solid Tumours (RECIST) guideline version 1.1 (R09-0262). In case of PD or response, tumour assessment should be repeated as per irRECIST (R15-2005). For details on lesion measurements and response assessment, see Appendix 10.3 RECIST 1.1 Criteria and Appendix 10.4 irRECIST.

Tumour response will be assessed by investigator review throughout the study and clinical decisions will be based on investigator assessment. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). In case of cutaneous metastases, these should be documented by colour photography including a ruler to estimate the size of the lesion.

RECIST Assessment of Disease
RECIST 1.1 will be applied as the primary measure for assessment of tumour response, date of disease progression, and as a basis for all protocol guidelines related to disease status.

irRECIST Assessment of Disease
After the first documentation of PD and if the patient is clinically stable, the investigator may decide that the patient may continue study treatment until confirmed PD. Imaging is repeated for confirmation ≥ 4 weeks later. The investigator or delegate will determine if the follow-up tumour imaging confirms PD (see Appendix 10.4).

irRECIST is based on RECIST 1.1, but adapted to account for the unique tumour response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumour response and progression, and make treatment decisions.

These data will be collected in the eCRF. If radiologic progression is confirmed by subsequent scan, the patient will be discontinued from trial treatment. If radiologic progression is not confirmed by irRECIST per the site, then the patients should continue on trial treatment and follow the regular imaging schedule intervals until progression is confirmed at a later time point by the site.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinical significant disease progression
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from trial treatment at first radiologic evidence of PD and is not required to have repeat tumour imaging for confirmation of PD by irRECIST. For patients who discontinue study therapy without documented PD, every effort should be made to continue monitoring their disease status by tumour imaging using the same imaging schedule used while on treatment, until the start of subsequent anti-

cancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 5.1.2: 1.

Table 5.1.2: 1 Imaging and treatment after first radiologic evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory tumour imaging by site by irRECIST	Repeat imaging at ≥ 4 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumour imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	Not applicable
Repeat tumour imaging shows unconfirmed PD by irRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumour imaging shows SD, PR, or CR by irRECIST per investigator asessment	Continue regularly scheduled imaging assessments*	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumour imaging should occur according to the regular imaging schedule

* In case of SD/PR/CR, patients do not need to undergo the next scheduled tumour imaging if it is less than 2 weeks later; tumour imaging may resume at the subsequent scheduled imaging time point.

5.2 ASSESSMENT OF SAFETY

The safety of afatinib in combination with pembrolizumab will be assessed by a descriptive analysis of incidence and severity of adverse events graded according to CTCAE version 4.03.

Safety run in
After the first 12 patients have been treated for at least one full cycle, the SMC (see Sections 3.1 and 8.7) will assess the overall safety profile and confirm the RP2D (refer to Section 4.1.2 and Figure 3.1: 2). In case 40 mg afatinib in combination with pembrolizumab is considered too toxic, ongoing patients on afatinib 40 mg will have their dose reduced to 30 mg and 12 more patients will be included in the safety run in with a starting dose of afatinib 30 mg once daily. After they have been treated for at least one full cycle, the SMC will assess the data and confirm the RP2D. In case the RP2D is confirmed as 30 mg, the patients will continue on this dose. In case 30 mg is considered too toxic, the trial will be stopped.

Main part
Once the RP2D of afatinib in combination with pembrolizumab has been established, this will be the starting dose of afatinib for any future patients entered to the trial (i.e. the main part). In total, 38 patients will be included in the main part.

5.2.1 Physical examination

A physical examination will be performed at the time points specified in the Flowchart.

A full physical examination serves as a clinical tumour assessment and should include a cardiopulmonary examination, examination of the regional lymph nodes, the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination should be clarified. Wherever possible the same investigator should perform this examination.

A limited physical examination should include a cardiopulmonary examination, a clinical tumour assessment, an examination of the regional lymph nodes, and an examination of the abdomen.

Measurement of height (in cm), body weight (in kg), and the evaluation of the ECOG performance status (see Appendix 10.7) will be performed at the time points specified in the Flowchart.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flowchart.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.

5.2.3 Safety laboratory parameters

Safety laboratory samples will be analysed at a local laboratory and the data will be manually entered in the eCRF. Safety laboratory examinations to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the Flowchart.

Thyroid function testing is to be performed as indicated in the flowchart while on treatment with pembrolizumab. Thyroid panel should include:

- Triiodothyronine (T3) or Free Triiodothyronine (FT3)
- Free thyroxine (FT4)

- Thyroid stimulating hormone (TSH)

Additional samples can be collected if clinically required at the discretion of the investigator. The date of assessment and results will be recorded on the patient's eCRF.

Table 5.2.3: 1 Safety laboratory tests

Category	Parameters
Hematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, reticulocytes, white blood cell count (WBC) with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils)
Coagulation	International Normalised Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Electrolytes	Sodium, potassium, calcium, magnesium, chloride, bicarbonate (HCO_3)
Liver function tests	Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin
Renal function parameters	Blood urea (preferred) or blood urea nitrogen (BUN), creatinine; creatinine clearance at screening if applicable*
Pancreatic function parameters	Amylase, Lipase
Other	Glucose, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, creatine phosphokinase (CPK)
Urinalysis	pH, protein, glucose, blood, leucocytes, nitrite; in case of pathological finding further evaluation should be performed and results documented
Pregnancy test	β-HCG testing in urine or serum in women of childbearing potential (WOCBP)
Thyroid function testing	Triiodothyronine (T3) or Free Triiodothyronine (FT3), Free thyroxine (FT4), Thyroid stimulating hormone (TSH)

* Creatinine clearance should be calculated per institutional standard. See also Appendix 10.6.

The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal and clinically relevant findings from these investigations need to be reported as an adverse event (please refer to Section 5.2.6.2).

Patients do not have to be fasted for the blood or urine sampling for the safety laboratory.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Sections 5.2.6.1 and 10.5 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the Flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Dose limiting toxicities

The occurrence of any of the below mentioned toxicities will be considered a DLT, if judged by the investigator to be related to study drug administration. DLTs occurring during the first 21-day period (Cycle 1) in the safety run in will be considered protocol specified AESI (see Section 5.2.6.1).

Table 5.2.5.1: 1 Dose Limiting Toxicities

Related toxicity category	**Criteria defining a DLT***
Hematologic	• CTCAE Grade 4 neutropenia lasting ≥ 7 days. • CTCAE Grade ≥ 3 documented infection with neutropenia. • CTCAE Grade ≥ 3 febrile neutropenia (ANC<1000/mm^3 complicated by fever ≥38.5°C or a sustained temperature of ≥38.0°C for more than 1 hour). • CTCAE Grade 3 thrombocytopenia associated with bleeding requiring transfusion. • CTCAE Grade 4 (<25,000/m^3) thrombocytopenia. • CTCAE Grade 4 anaemia.
Non-hematologic	• Any Grade ≥ 3 non-hematologic (not laboratory) toxicities lasting >3 days despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator. • Any Grade 3 or Grade 4 non-hematologic laboratory value if: - Medical intervention is required to treat the patient, or - The abnormality leads to hospitalization, or - The abnormality persists for >1 week. - Exceptions: Clinically non-significant, treatable, and reversible laboratory abnormalities including liver function tests, uric acid, etc. • Grade ≥ 2 ILD. • Grade ≥ 2 colitis. • Grade ≥ 2 renal failure or nephritis.

	• Any grade 5 event. • 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. • An elevated AST or ALT lab value that is greater than or equal to 5X the upper limit of normal and an elevated total bilirubin lab value greater than or equal to 2X upper limit of normal measured in the same blood draw sample, with the exclusion of causes due to underlying diseases (for patients with elevated liver enzymes at baseline).
Re-Treatment Delay	• Any related toxicities that result in a > 14 days delay in initiating Cycle 2 Day 1 dosing with afatinib and/or pembrolizumab. • Patients who miss more than 5 days of therapy for treatment related toxicity at first cycle.

*It is the responsibility of the investigator to follow-up on these in a timely manner.

The RP2D confirmation will be based on DLTs observed during the first cycle of the safety run in from the patients treated with a starting dose of 40 mg afatinib or 30 mg afatinib (in case the 40 mg is considered too toxic) (see Appendix 10.9.3). However, all DLT observed in all treatment cycles will be considered for re-estimation of the RP2D based on the BLRM as a sensitivity analysis. To obtain this, the model might be re-run including the DLT information from all cycles. Based on both RP2D estimates, the recommended dose for further development will be selected. In regular intervals, all available safety data including adverse events qualifying for DLT will be submitted to the SMC.

5.2.5.2 Performance status

With the early termination of the study, the evaluation of the ECOG performance status is no longer performed.

Evaluation of the ECOG performance status will be performed at the time points specified in the Flowchart. The ECOG performance status (also called the WHO or Zubrod score) is found in Appendix 10.7.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation; or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity; or
- is a congenital anomaly / birth defect; or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered "Always Serious"

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and **AE reporting to sponsor and timelines**". Note: PD of the underlying malignancy and without a causal relationship between the study drug and the PD are reported as a study endpoint and as such is exempted from reporting as an (S)AE (see later in Section 5.2.6).

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" will be made available to the investigators. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs will be reported on the eCRF/SAE reporting forms, as per the SAE reporting instructions detailed in the 'Adverse Event Reporting' Section of the ISF. AESI are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria.

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

For patients with normal liver function (ALT, AST, bilirubin within normal limits) at baseline:

- 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*.

For patients with abnormal liver function at baseline (AST and/or ALT>ULN)):

- An elevated AST or ALT lab value that is greater than or equal to 5X the upper limit of normal and an elevated total bilirubin lab value greater than or equal to 2X upper limit of normal measured in the same blood draw sample, with the exclusion of causes due to underlying diseases.

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the sponsor representative. However, abnormalities of liver blood tests that do not meet the criteria noted above are not AESIs for this trial.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the “DILI checklist” provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Dose Limiting Toxicities

Dose Limiting Toxicities (DLT) occurring during the first cycle in patients included in the safety run in will be considered protocol specified AESI. See Table 5.2.5.1: 1 for DLT definitions.

Overdose

For this trial, an overdose will be defined as any dose of 1000 mg or ≥5 times the indicated dose of pembrolizumab.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

An overdose, that is not associated with clinical symptoms or abnormal laboratory results, also needs to be reported.

Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Causal relationship of AEs

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

With the early termination of the study, AESIs, AEs and SAEs are not collected and documented in the eCRF after the end of the REP for pembrolizumab and afatinib.

Investigators will report all deaths/fatal AEs regardless of relationship, until the end of the REP only. After the REP, investigators only report SAEs and AESIs related to afatinib that the investigator becomes aware of.

The following must be collected, documented on the appropriate eCRF(s) by the investigator:

For pembrolizumab:

- From signing the informed consent onwards until the end of treatment, which includes the REP:
  - All AEs (non-serious and serious) and all AESIs.
- After the end of the REP until the individual subject's end of trial, 90 days after last dose of pembrolizumab or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier:
  - All SAEs.

For afatinib

- From signing the informed consent onwards until the end of treatment, which includes the REP:
  - All AEs (non-serious and serious) and all AESIs.
- After the end of the REP until the individual subject's end of trial or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier:
  - All AESIs related to afatinib and all SAEs.
- After the subject initiates new anticancer therapy (if applicable) and until the individual subject's end of trial:
  - All AESIs and SAEs related to afatinib.
- After the individual patient's end of the trial:
  - The investigator does not need to actively monitor the patient for AEs but should report SAEs and AESIs related to afatinib of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the eCRF.

See also Figure 5.2.6.2: 1 and 5.2.6.2: 2.

The rules for Adverse Event Reporting exemptions still apply.

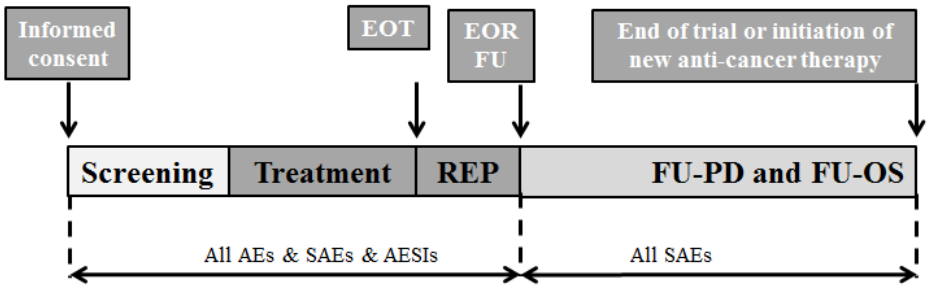


Figure 5.2.6.2: 1 AE reporting process for pembrolizumab

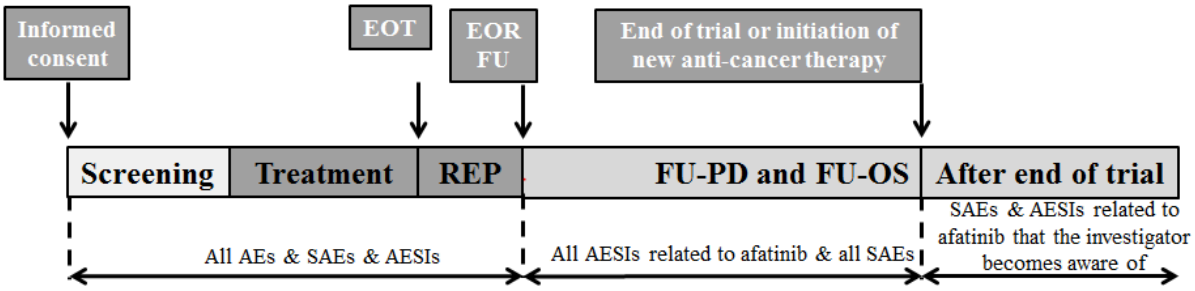


Figure 5.2.6.2: 2 AE reporting process for afatinib

Patients, who discontinue trial medication prematurely and agree to be contacted further, should be followed up as described in Section 3.3.4.1. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, in addition to requirements outlined in Figure 5.2.6.2:1.

The Residual Effect Period (REP) is defined as 30 days for both afatinib and pembrolizumab. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.4.

Events which occur after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the eCRF and BI SAE form (if applicable):

- Worsening pre-existing conditions other than underlying disease.
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected as such in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

Information about pregnancy of female patients of childbearing potential and female partners of male trial participants that occur from the time of treatment allocation through 120 days following the last dose of pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. This reporting period is 2 weeks after last afatinib treatment in case of monotherapy treatment with afatinib.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

Exemptions to SAE reporting
Protocol specified outcome events should be collected on the appropriate eCRF page only.

Disease Progression is a study endpoint for analysis of efficacy, and as such is exempted from reporting as an (S)AE. Progression of the patient's underlying malignancy will be recorded in the appropriate pages of the (e)CRF as part of efficacy data collection and will not be reported on the (S)AE form. Death due to disease progression is also to be recorded on the appropriate (e)CRF page and not on a SAE form. It will therefore not be entered in the safety database.

However, when there is evidence suggesting a causal relationship between the study drug and the progression of the underlying malignancy, the event must be reported as (S)AE on the eCRF and on the SAE form.

Examples of exempted events of PD are:

- Progression of underlying malignancy (PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD).
- Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Exempted events are monitored at appropriate intervals during Medical and Quality Review Meetings (MQRMs).

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood samples will be collected from all patients on the days of 2nd (C2_V) and 3rd (C3_V) infusion of pembrolizumab, at the time points described in Appendix 10.1 (Table 10.1.2: 1) in order to assess the pharmacokinetics of afatinib and pembrolizumab.

The objective of afatinib PK assessment is to characterize the impact of pembrolizumab comedication on steady state parameters of afatinib as determined by steady state pre-dose plasma concentrations (Cpre, ss) on day 22 and 43 of treatment, respectively.

5.3.2 Methods of sample collection

PK blood sampling will be performed as described in Appendix 10.1. For quantification of drug concentrations of afatinib 1 x 2 mL of venous blood will be collected at each PK blood draw. For quantification of drug concentrations of pembrolizumab 1 x 3.5 mL of venous blood will be collected at each PK blood draw.

Date and clock time of drug administration, as well as blood collection times at all visits where PK sampling is performed must be recorded in the eCRF.

Correct, complete, and legible documentation of drug administration and blood sampling times as well as adequate handling and identification of PK samples (the labels of the PK tubes have to contain at minimum: study number, visit number, patient number, and planned time) is mandatory to obtain data of adequate quality for the pharmacokinetic analysis. In order to prevent instabilities of PK samples special precautions have to be taken during collection, handling, storage, and shipment of PK samples. A freezer temperature log must be maintained if samples are being stored at any time until shipment. Detailed instructions are provided in the lab manual.

5.3.3 Analytical determinations

Afatinib drug concentrations will be determined by a validated high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay. The procedure and specification of the analytical method are available at the analytical laboratory

PK blood samples for pembrolizumab will be stored and pembrolizumab drug concentrations will be determined by upon request.

5.3.4 Pharmacokinetic – pharmacodynamic relationship

No pharmacokinetic-pharmacodynamic relationship investigation is planned.

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. The provision of a tumour sample for central PD-L1 assessment and correlative studies is also described in Section 3.3.2.

Handling of Samples and Biomarker Results
Detailed instructions for handling, storage, and shipment of the biomarker samples will be provided in the laboratory manual included in the ISF. All required materials and labels will be provided. For the mandatory sample obtained at screening, a fresh biopsy is preferred and freshly cut slides should be immediately submitted to the testing laboratory.

A brief description of the biomarker analyses to be performed is provided here. The results of the analyses will not be directly reported to investigators.

5.4.1 Tumour tissue samples

All tumour samples will be obtained at the time points as defined in the Flowchart and Appendix 10.2.

Tumour Tissue Sample at Screening Visit (Mandatory):
As described in Section 3.3.2, patients cannot be enrolled in the study if they are unable to provide a sample of their tumour. A sample of a fresh biopsy is preferred but archival tumour tissue can also be used. Tumour samples should be provided in the form of a formalin-fixed paraffin embedded (FFPE) block (preferred) or less preferably in the form of a mandatory minimum of 10 slides of unstained 4-5-micron sections from the FFPE tumour block.

The tumour tissue sample will be used to (i) measure the expression of the protein PD-L1 by means of an immuno-histochemical (IHC) assay and (ii) to measure the mRNA expression of genes involved in the immune system.

Tumour Biopsy for Exploratory Analysis at screening (Optional):
For patients who agreed to exploratory biomarker testing and if local regulations allow, excess tissue obtained at screening may be used to further address scientific questions as new information in regard to the disease or the study drug becomes available. These analyses might comprise but are not limited to the further evaluation of the patient's immune status by determination of tumour infiltrating cells (e.g. CD8+ cells) or TH1-type cytokines.

Any leftover samples from the study will be stored at Boehringer Ingelheim or contract research organization for up to 3 years after final study report.

5.4.2 Blood samples for biomarker analyses

With the early termination of the study, there will be no exploratory retrospective assessment of biomarkers in blood samples.

Participation in blood sampling for biomarkers is voluntary and not a prerequisite for participation in the trial but is highly encouraged. Blood samples for biomarkers will be taken only after a separate informed consent has been given in accordance with local ethical and regulatory requirements. Blood samples (~19 mL) for biomarker analysis should be taken as specified in the Flowchart.

The blood samples may be utilised for the measurement of the levels of proteins in the blood, or on the surface of blood cells, which may be of prognostic or predictive relevance to the patients' response to the study medications. For example, the measurements of cytokine levels in the blood may be informative of the patient's immune response following the administration of medication or the measurement of plasma protein levels using the immunostrat (Biodesix) technology may be informative in identifying patients likely to receive maximum benefit from the treatment.

Blood samples for biomarker analyses will be stored at Boehringer Ingelheim or contract research organization for up to 3 years after final study report.

Methods and timing of sample collection:

Sampling will be performed at the time points specified in the Flowchart.

Plasma

Approximately 10 mL blood will be drawn into an EDTA blood collection tube.

Serum

Approximately 8.5 mL blood will be drawn into a serum separation tube.

For all biological samples collected, detailed instructions on sampling, preparation, processing, shipment, and storage are provided in the laboratory manual.

5.5 OTHER ASSESSMENTS

Not applicable.

5.6 APPROPRIATENESS OF MEASUREMENTS

All clinical assessments are standard measurements commonly used in studies of advanced solid tumours. RECIST version 1.1 (R09-0262) and irRECIST (R15-2005) are used for assessment of the change in tumour burden. These criteria are well established and well received by the regulatory authorities and scientific community.

The US National Cancer Institute (NCI) CTCAE is used in the assessment of adverse events in cancer patients. In the present trial CTCAE version 4.03 will be used.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

With the early termination of the study, patients are no longer followed for progression or survival after study treatment completion. A patient is considered to have completed the trial after the REP visit.

Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed consent may be signed by the patient prior to the screening visit. A separate written informed consent must be obtained before the collection of blood samples for biomarkers and before shipment of tumour tissue for biomarker testing.

Eligible patients will receive the study treatment for up to 35 cycles (about 2 years) or until any of the criteria for stopping medication are met (see Section 3.3.4.1). During the treatment phase, visits should be performed on week one, week three, and then every three weeks, but within three days of the scheduled date. The scheduled time interval for each visit is relative to the initiation of trial medication. Following discontinuation of both trial medications, patients will be followed at EOT visit at the end of the residual effect period. Then the patient will enter the follow-up period until trial completion. Please see the Flowchart for the visit schedule.

Unscheduled visits can be performed as necessary and assessments will be performed as required at the discretion of the investigator. In case a patient missed a visit and the patient reports to the investigator between the missed visit and the next scheduled visit, the date of the report and the reason for the delayed visit should be noted in the patient's chart. The next visit, however, should take place at the scheduled time. In the event of any interruption/delay of treatment, the imaging schedule should not be changed.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The assessments to be performed at the respective visits are outlined in the Flowchart and the procedures for each assessment are described in detail in Section 5.

6.2.1 Screening and run-in period(s)

Screening Period
The screening visit should be performed within 28 days before the first administration of treatment.

Before or during the screening visit, prior to any study procedures, all patients will need to sign the Informed Consent Form (ICF) for trial participation.

Examinations and assessments will be conducted as depicted in the Flowchart. Patients' medical history and demographic information will be collected and in- and exclusion criteria must be assessed. Details are given below.

A tumour tissue biopsy will be submitted to the central laboratory. This is a mandatory requirement for study enrolment.

Demographics to be collected during the screening visit are:

- Gender;

- Date or year of birth (in accordance with local laws and regulations);
- Race (in accordance with local laws and regulations);
- Alcohol history;
- Histological subtype.

The smoking history will be documented as smoking status defined as:
- Never smoker with <100 cigarettes/lifetime;
- Current-smoker;
- Former smoker.

Baseline Conditions
Baseline conditions and concomitant therapies present during screening will be recorded in the eCRF.

Medical History:

Medical history of NSCLC will be obtained during screening and reported in the eCRF:
- The date of first histological diagnosis;
- The primary tumour site;
- The number and location of metastatic sites at screening (bone, brain, liver, pleural effusion, other);
- Previous treatment for NSCLC, including any surgery, radiotherapy, and or systemic therapy, including start and end dates and the outcome.

Baseline imaging
If images are available from before the obtainment of the informed consent and the images are within 28 days of start of treatment and performed as part of routine clinical practice, imaging does not need to be repeated at the screening visit, provided it is clear from source documents that the imaging was not performed for the purpose of the present trial.

6.2.2 Treatment period(s)

Eligible patients will be administered study medication in 21 day treatment cycles until criteria for treatment discontinuation are met (see Section 3.3.4). The EOT visit should be performed for all patients after permanent discontinuation of both trial treatments (see the Flowchart for time window).

Treatment visits are specified in the Flowchart and must be conducted as scheduled and outlined there.

PK blood samples are drawn just before administration of afatinib and infusion of pembrolizumab at C2_V and C3_V as specified in Section 10.1.

6.2.3 Follow-up period and trial completion

With the early termination of the study, patients are no longer followed for progression or survival after study treatment completion. A patient is considered to have completed the trial after the REP visit.

After the end of study treatment (EOT), all patients are required to attend the end of the residual effect period (EOR) visit to evaluate safety. The Residual Effect Period (REP) is defined as 30 days for both afatinib and pembrolizumab. During the REP one visit is

conducted as indicated in the Flowchart. In case only one of the trial medications is discontinued, the patient is considered as still being in the treatment period; however, the individual termination of trial medication eCRF page must be completed when either is discontinued. The purpose of this follow-up visit is primarily to collect all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT. For the majority of patients, disease progression will already be documented at this point. However the REP follow-up visit should occur for all patients, including those patients with disease progression and/or start of subsequent anti-cancer treatment.

For AE reporting after EOT, see Section 5.2.6.2.

After study treatment completion, further therapy will be decided by the investigator including continuation of afatinib (using commercial products), alternative therapy, or best supportive care.

Follow-up for progression
If a patient does not have documented disease progression or did not start subsequent anti-cancer treatment during the trial treatment or REP, he/she will continue to have regular follow-up visits (FU-PD) and tumour assessments according to the Flowchart. The end of FU-PD will occur at the time point of disease progression or start of subsequent anti-cancer treatment, whichever occurs first.

Follow-up for survival
After disease progression and/or start of subsequent anti-cancer treatment, the patient will enter the Follow-up for survival (FU-OS) period. No visits will be performed for the purposes of the trial, but data on further treatment and survival will be collected from medical records or via telephone.

Data will be collected as detailed in the Flowchart and may also be collected at additional time points when a snapshot of data is required (e.g. at the time of the primary analysis). Data collection will continue until death, lost-to follow-up, patient refusal, withdrawal of consent for collection of overall survival data, or completion of the whole trial (as specified in Section 8.6) whatever occurs earlier.

If a patient cannot be contacted for vital status, information may also be obtained by other means in accordance with local regulations, e.g. contact with patients' health care providers, public sources, e.g. death registry, obituary listing, etc. when it is available and verifiable.

6.2.4 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:
- Lost to follow-up.
- Refuse further follow-up.
- Withdrawal of consent.
- Death.
- The trial is ended as described in Section 8.6.

In that case, the Final Visit (FV) is completed in the eCRF; however, the patient does not necessarily need to attend a visit at the site. Refer to Section 3.3.4.1 for instructions on when to withdraw an individual patient from trial treatment.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is an exploratory, open label, non-randomised, phase II trial of afatinib in combination with pembrolizumab in patients with squamous NSCLC, who progressed during or after first line platinum-based standard therapy and have received no prior treatment with a checkpoint inhibitor or EGFR targeted therapy.

The primary objective of the trial is to assess the efficacy of afatinib in combination with pembrolizumab, as measured by objective response OR.

Based upon these design considerations, descriptive summaries of efficacy endpoints will be produced. If the starting dose is reduced from 40 mg to 30 mg, the main efficacy summaries will be produced on the patients with a starting dose of 30 mg.

The dose confirmation will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R13-4806, R13-4803). Further details about this model can be found in Appendix 10.9.

This model will be used to evaluate the adverse events occurring during the first treatment cycle and will serve as guidance for the SMC when deciding on the dose to be used in the remaining patients that are to participate in the trial. Please also see Section 5.2.5.1 for details on DLTs and information on which ones will be used for the BLRM evaluations. Other criteria evaluated by the SMC are described in Section 3.1.

7.2 NULL AND ALTERNATIVE HYPOTHESES

As an exploratory Phase II trial, inferences about the efficacy of afatinib when given in combination with pembrolizumab will be based on the magnitude of the observed OR and other efficacy endpoints (e.g. PFS, DoR), rather than formal hypothesis testing.

7.3 PLANNED ANALYSES

In order to expedite the reporting of the primary efficacy endpoint of OR, two analysis time points are defined, and all efficacy and safety endpoints will be analysed at each time point. The first analysis will be performed when all treated patients have either reached the fourth imaging time point (week 36) or have been withdrawn from the trial, whichever occurs earlier.

A second and final analysis time point will take place when the trial has reached its completion. See Section 8.6 for the definition of the end of the trial.

The primary analyses of efficacy and safety will be performed on the patients treated with the RP2D as starting dose. This will consist of all patients receiving at least one dose of afatinib (at the starting RP2D) and/or pembrolizumab. All data collected by the primary analysis time point, will be included.

No per protocol set will be used for the analyses. However, important protocol violations will be summarised, these will be specified in the trial statistical analysis plan (TSAP).

All imaging related endpoints will be investigator assessed primarily according to RECIST 1.1. Supportive summaries will also be produced without the supplemented irRECIST criteria.

7.3.1 Primary endpoint analyses

In this exploratory study objective response (OR) is defined as the primary endpoint of interest. The analysis will be based on treated patients, based upon the starting dose they have been taking.

For OR status tumour imaging will be performed until the earliest of disease progression, death, or last evaluable tumour assessment before the start of subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent. OR will be analysed in terms of OR rate (ORR), defined as the proportion of patients with best overall response of CR or PR as determined by RECIST 1.1. The ORR will be calculated and presented with 95% two-sided confidence intervals using the exact Clopper-Pearson method. In addition, frequencies and percentages are also shown. As per RECIST 1.1 (R09-0262) guidance confirmation of OR is a requirement for this trial.

The analysis of the primary endpoint will be repeated in the following subgroups:

- PD-L1 status (<1%, 1-49%, ≥50%)
- Subgroups defined by the biomarkers related to immune status
- Other sub groups may be defined in the TSAP

7.3.2 Secondary endpoint analyses

All secondary endpoints will be evaluated.

Disease control (DC)
DC will be analysed in terms of DC rate (DCR), defined as the proportion of patients with best overall response of CR, PR, or SD according to RECIST 1.1. Proportions will be presented with 95% two-sided confidence intervals using the exact Clopper-Pearson method. In addition, frequencies and percentages are also shown.

Duration of objective response (DoR)
For all patients with an OR the duration of OR will be calculated as follows:
For patients with disease progression or death:

- Duration of OR [days] = date of outcome – date of first assessment indicating OR + 1

For patients without disease progression or death:

- Duration of OR (censored) [days] = date of outcome – date of first assessment indicating OR + 1

The censoring rules for OR (i.e. outcome and date of outcome) will be described in the TSAP. The outcome will be assessed according to RECIST 1.1.

Kaplan-Meier estimates will be used to display the distribution of DoR with 95% confidence intervals, using Greenwood's variance estimate. Kaplan-Meier estimates will be used to calculate median duration of OR.

Progression-free survival (PFS)
PFS is defined as time from first drug intake until disease progression or death from any cause, whichever occurs earlier. The date of progression will be based on the investigator assessment according to the RECIST 1.1.

For patients with 'event' as an outcome for PFS:

- PFS [days] = date of outcome – date of start of treatment + 1

For patients with 'censored' as an outcome for PFS:

- PFS (censored) [days] = date of outcome – date of start of treatment + 1

The censoring rules for PFS (i.e. outcome and date of outcome) will be described in the TSAP.

Kaplan-Meier estimates will be used to display the distribution of PFS with 95% confidence intervals, using Greenwood's variance estimate.

Overall survival
For patients with known date of death (any reason):

- Overall survival [days] = date of death – date of start of treatment + 1

For patients known to be alive by the end of trial or follow-up period:

- Overall survival (censored) [days] = date of last visit when patient is known to be alive – date of start of treatment + 1

Patients with unknown OS status or date will be handled as described in the TSAP.

Kaplan-Meier estimates will be used to display the distribution of OS with 95% confidence intervals, using Greenwood's variance estimate.

Tumour shrinkage
Tumour shrinkage measured as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of longest diameters of the same set of target lesions will be analysed using mean and standard deviation. Maximum percentage decreases will also be summarised, including waterfall plots.

All secondary endpoint analyses related to efficacy will be repeated in the following subgroups:

- PD-L1 status (<1%, 1-49%, ≥50%)
- Subgroups defined by the biomarkers related to immune status

Recommended Phase II Dose
The dose confirmed by the SMC based on the process and parameters described in Section 1.4, Section 3.1, and Section 5.2.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 30 days after end of last trial drug administration, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis, based upon the starting dose they have been taking. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges as well as by evaluations based on CTCAE grading. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Adverse events as well as laboratory parameters will be graded according to CTCAE, version 4.03 (R15-5988).

Standard tabulations arranged by MedDRA SOC and PT will include:

- The overall incidence and severity of adverse events,
- AE judged to have been related to study drug
- AE leading to dosage reduction
- AE leading to permanent treatment discontinuation

- SAE
- Fatal outcome

Additional more in-depth analyses of AEs and laboratory data will be performed as needed and detailed in the TSAP.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Please refer to Section 7.3.3 for the description of the planned PK analysis.

7.3.6 Biomarker and pharmacogenetic analyses

Primary and secondary measures of clinical efficacy will be assessed by PD-L1 status, see Section 2.2.1.

The mRNA expression of genes involved in the immune system will be investigated descriptively and its association to measures of clinical efficacy will be explored.

Additional exploratory biomarker analyses, e.g. of mutations related to the emergence of resistance, will be defined in a statistical analysis plan, if deemed necessary.

7.4 INTERIM ANALYSES

No interim analysis is planned, however after 12 patients have been entered into the study, have received 40 mg afatinib + 200 mg pembrolizumab, and have completed at least their first cycle of treatment, the SMC will evaluate and confirm whether 40 mg of afatinib in this combination trial is an adequate RP2D, or whether 30 mg afatinib should be the starting dose for any patient treated with this combination. In case the RP2D is not confirmed as 40 mg afatinib in combination with pembrolizumab, there will be a second safety run in and the SMC will evaluate and confirm the RP2D after 12 patients in the second safety run in have completed at least their first cycle of treatment at 30 mg dose level.

A clinical safety summary will be created on the basis of the safety run in.

This decision will be taken using the safety criteria defined in Section 5.2.5.1 and analysed with a BLRM (see Section 3.1 and Appendix 10.9 for details), efficacy criteria (see Section 2.1 for more details), and the totality of the patients' data. The evaluation of the safety criteria has to be taken in a non-binding sense and will serve as guidance for the decision making process of the SMC.

7.5 HANDLING OF MISSING DATA

In general, missing data will not be imputed.

For PFS and OS, every effort will be made to obtain date of progression or death for patients known to have progressed or died. Detailed censoring rules will be specified in the TSAP.

For partial or missing AE onset and/or end dates, BI internal rules will be followed for imputation (see Reference Document 001-MCG-156_RD01 "Handling of missing and incomplete AE dates").

Pharmacokinetics:
Pharmacokinetic parameters: In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time 0 and the first time point with a concentration above the quantification limit. All other BLQ and NOP values of the profile will be ignored. Descriptive statistics of parameters will be calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

This is an open label, non-randomised, single-arm trial of afatinib in combination with pembrolizumab.

7.7 DETERMINATION OF SAMPLE SIZE

The expected ORR with single agent afatinib is approximately 6% (P15-06906) and with single agent pembrolizumab approximately 18% (R15-6023). It is anticipated that the combination of the two agents will have an ORR of approximately 30-40%. With 50 evaluable patients an ORR of 30% or more would be observed with a probability of about 81% assuming a true response rate of 35%. The probability to observe a false positive signal, e.g. to observe at least an ORR of 30% if the underlying true ORR is 18%, is around 3%. Table 7.7: 1 summarises the probabilities of observing certain ORRs based on different assumptions of the underlying ORR.

As such it is planned to treat 50 patients at the RP2D. If 40 mg is chosen as the starting RP2D then only 50 treated patients will be required, however if 30 mg is chosen as the starting RP2D then up to 62 treated patients may be required (12 at 40 mg and 50 at 30 mg). In case the 30 mg is considered too toxic, the trial will be stopped and in that case 24 patients will be required.

Table 7.7: 1 Probabilities of observing certain objective response rates

True underlying OR rate	Patients	Probability to observe at least		
		ORR≥25% (≥13 ORs)		
40%	50	98.7%	40%	50
35%	50	93.4%	35%	50
30%	50	77.7%	30%	50
18%	50	10.2%	18%	50

Note: Exact binomial probabilities calculated in SAS v9

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report (CTR).

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

A separate informed consent to allow exploratory biomarker analyses on blood samples as well as tumour biopsies must be given in accordance with local ethical and regulatory requirements.

The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form if required as per local IRB/IEC. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see Section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations).
- Patient participation in the trial (substance, trial number, patient number, date patient was informed).
- Dates of patient's visits, including dispensing of trial medication.
- Medical history (including trial indication and concomitant diseases, if applicable).

- Medication history.
- Adverse events and outcome events (onset date (mandatory) and end date (if available))
- Serious adverse events (onset date (mandatory) and end date (if available)).
- Concomitant therapy (start date, changes).
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available).
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review, and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

Exemptions from expedited reporting are described in Section 5.2.6.2, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage, and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95).
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

Last Patient Last Visit Primary Endpoint (LPLV PE): The primary analysis will take place four imaging cycles after the last patient entered the trial.

The end of the trial is defined as the date of the last visit (Final Visit) of the last patient in the trial ("Last Patient Out"). All patients must have completed (or been prematurely withdrawn from) study treatment and attended end of the residual effect period visit. All patients must also have had a minimum of 24 months vital status collection from study entry (unless prematurely withdrawn from study). The trial will be completed about 27 months after last patient entered the trial. With the early termination of the study patients will not need 24 months of vital status collection. The end of the trial is defined as the date of the REP visit for the last patient.

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The study will be performed by investigators specialised in the treatment of lung cancer. The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Safety Monitoring committee (SMC) composed of sponsor representatives, coordinating investigator, and two to three other investigators will be established to review individual and aggregated safety and efficacy data at regular intervals to determine the safety profile and benefit/risk ratio and recommend the RP2D. The SMC may also provide recommendations to further enhance safety, e.g. regarding patient selection/ recruitment/dose adjustments, or request additional safety analysis. External experts may be appointed as needed. The sponsor will review the recommendations of the SMC and make the final decision. Details of the SMC responsibilities and procedures are described in the SMC charter.

Relevant documentation on the participating (Principal) investigators (e.g. their curricula vitae) will be filed in the Investigator Site File (ISF). The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs,
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial,

- Ensure appropriate training and information of Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service for the analysis of biomarkers, logistics of such tissue/blood samples, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

To evaluate the effect of pembrolizumab on afatinib pharmacokinetic (PK) properties, pre-dose PK samples will be taken of all patients.

PK sampling afatinib:

- C2_V and C3_V day 1 pre-dose, shortly before administration of afatinib & pembrolizumab (e.g. -0:05)

Additional PKsamples for pembrolizumab will be taken, which may be analysed upon request.

PK sampling pembrolizumab:

- C2_V and C3_V day 1 pre-dose, shortly before administration of afatinib & pembrolizumab (e.g. -0:05)

Endpoints and Analyses (afatinib)

- Listings of Cpre,ss values at day 22 and 43 of treatment, respectively
- Historical comparison

10.1.1 Handling procedure of blood samples for plasma concentration-time measurements

Drug concentration-time profiles: Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), BLQ (below the limit of quantification) and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (including the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range.

Pharmacokinetic parameters: In the non-compartmental analysis, concentration data identified with NOS, NOR and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time 0 and the first time point with a concentration above the quantification limit. All other BLQ and NOP values of the profile will be ignored. Descriptive statistics of parameters will be calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

10.1.2 Time schedule for pharmacokinetic blood sampling

Table 10.1.2: 1 Time schedule for PK blood sampling

Treatment Period	Visit	Time Point	PlannedTime [hh:min]	Event	Afatinib	Pembrolizumab
Cycle 2	C2_V	Shortly before drug administration	-0:05	PK Blood	X	X
Cycle 3	C3_V	Shortly before drug administration	-0:05	PK Blood	X	X

10.2 TRIAL BIOMARKER PLAN

The details of the biomarker aspects are described in Section 5.4. The analyses of biomarkers are described in Section 7.3.6. The optional biomarker sampling is strongly recommended.

With the early termination of the study, the optional blood sample at the time of PD will not be collected.

Table 10.2: 1 Time schedule for biomarker sampling

Type of sample	Visit	Time point	Planned Time [hh:min]	Planned analyses	Mandatory or Optional
Tumour tissue	SV	Screening	NA	• PD-L1 • mRNA expression of genes involved in the immune system	Mandatory
	SV	Screening (excess tissue)	NA	• Exploratory analyses	Optional
Blood (plasma and serum)	C1_V1	C1_V1 prior to first drug administration	-0:05	• Exploratory analyses	Optional
	C4_V	C4_V	NA	• Exploratory analyses	Optional
	EOT or FU-PD	At time of PD	NA	• Exploratory analyses	Optional

10.3 RECIST 1.1 CRITERIA

The criteria below are based on RECIST 1.1 (R09-0262).

Tumour assessments should include CT scans of the chest and abdomen and a brain MRI at screening. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, bone) using an appropriate method (CT scan, MRI or bone scan) should be performed. The same radiographic procedure must be used throughout the study. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray, CT scan, MRI or bone scan) should be performed. Correlative imaging should then be repeated at each tumour assessment.

The preferred method of assessment is a spiral CT scan with i.v. and oral contrast, unless i.v. and/or oral contrast are medically contraindicated. Scans of the abdomen, pelvis and other areas of the body, but not chest, may be done with MRI instead of CT.

Skin lesions followed as target lesions must be documented by colour digital photography and must include in the image a ruler with millimetre subdivisions and a label that includes the patient's ID and date.

Bone scans (using ^{99}m-technetium polyphosphonate scintigraphy) are recommended at baseline if the patient has any signs and symptoms consistent with bone metastasis or a history of bone metastasis. Bone metastasis identified at baseline must be documented and assessed according to RECIST 1.1 at the times of the other tumour measurements indicated in the Flowchart. During the study bone scans should be repeated as clinically indicated in patients without bone metastasis at Baseline.

For the purposes of this study, patients should be re-evaluated for response every 9 weeks (63 ± 7 days). In the event of a treatment delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule.

Follow-up tumour assessments must utilize the same CT/MRI/photographic method and acquisition technique (including use or non-use of i.v. contrast) as were used for screening assessments to ensure comparability. A chest x-ray or skeletal x-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of CT/MRI/bone scan.

Only those patients who have measurable disease present at baseline, have received at least 3 weeks of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Measurability of tumour at baseline

Measurable lesions
Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray). Pathological lymph nodes, defined as lymph nodes with a short axis >15 mm are also measurable.

Measurable disease
Measurable disease requires the presence of at least one measurable lesion. Measurable lesion if limited to either small (<2 cm) solitary visceral lesion or scant (<5 cm) lymph nodes only

metastasis should be evaluated for additional evidence of malignant nature and discussed with the sponsor before enrolling.

Non-measurable disease
Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement or <20 mm with chest X-ray or pathological lymph nodes with shortest axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly unmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

New lesions in irradiated fields
At baseline, previously irradiated lesions should not be used as indicator lesions unless they have progressed since irradiation. New lesions occurring in previously irradiated fields can be used as indicator lesions.

Methods of measurement

All measurements must be recorded in metric notation, using a ruler or callipers. All baseline evaluations must be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment. If a lesion is considered too small to measure, a default measurement of 5 mm should be applied. If the lesion is not visible, a default measurement of 0 mm should be applied.

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is obligatory.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis.

Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.

Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours where known residual benign tumours can remain).

Baseline Documentation of Target and Non-target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and will be recorded, measured (longest diameter (LD) for all lesions except lymph nodes, where shortest diameter (ShD) is used) and numbered at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate

repetitive measurements (either by imaging techniques or clinically). Lymph nodes must be ≥15 mm in order to be considered as target lesions.

A sum of diameters (SoD) for all target lesions will be calculated (using ShD for lymph nodes and LD for all other lesions) and reported as the baseline SoD. The baseline SoD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.3: 1).

Table 10.3: 1 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the SoD of target lesions taking as reference the baseline SoD.
Progression (PD)	At least a 20% increase in the SoD of target lesions, taking as reference the smallest SoD recorded on study (including baseline), together with an absolute increase in the SoD of at least 5 mm. OR The appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR, taking as reference the baseline SoD, nor sufficient increase to qualify for PD taking as reference the smallest SoD recorded on study (including baseline).

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent” (see Table 10.3: 2).

Table 10.3: 2 Evaluation of non-target lesions and new lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesions or/and maintenance of tumour marker level above normal limits.
Progression (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel (or study chair).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Confirmation

In case of PD, confirmation will be performed with a repeat assessment ≥ 4 weeks after the RECIST criteria for response have been met.

In case of tumour response (CR or PR) confirmation will be performed with a repeat assessment at the next imaging time point (or ≥4 weeks later). An additional assessment in addition to the scheduled assessments is not expected. In the case of SD, measurement must have met the SD criteria at least once after study entry at an interval of not less than 6 weeks.

Evaluation of best response to study treatment

The best response to study treatment (Table 10.3: 3) is the best response recorded from the start of treatment until disease progression and/or start of subsequent anti-cancer treatment (taking as reference for progressive disease the smallest SoD recorded on study). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria (Table 10.3: 3).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10.3: 3 Algorithm for evaluation of overall response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.4 IMMUNE RELATED RECIST (IRRECIST)

RECIST 1.1 will be adapted to account for the unique tumour response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce anti-tumour effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumour burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

After first documentation of PD or response and if the patient is clinically stable, the patient may continue study treatment until confirmed PD. Confirmatory imaging may be performed ≥ 4 weeks later. Please also see Table 5.1.2: 1.

If repeat imaging shows < 20% tumour burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed.

If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study therapy.

In determining whether or not the tumour burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumour burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir.
- Non-target disease resulting in initial PD is worse (qualitative).
- New lesion resulting in initial PD is worse (qualitative).
- Additional new lesion(s) since last evaluation.

For patients who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a patient on study treatment until repeat imaging is obtained (see Table 5.1.2: 1). This decision by the investigator should be based on the patient's overall clinical condition

Clinical stability is defined as following:

- Absence of signs and symptoms indicating disease progression.
- No decline in ECOG performance status.
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per irRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study

treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumour imaging should continue to be performed following the intervals as outlined in Flowchart and Appendix 10.3.

When feasible, patients should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumour flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease (R15-2005).

10.5 CLINICAL EVALUATION OF LIVER INJURY

10.5.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.6.1 (Adverse Events of Special Interest), are to be further evaluated using the following procedures:

10.5.2 Procedures

Any elevation of ALT/AST and bilirubin qualifying as laboratory alert should be confirmed using the initial sample if possible.

If the alert is confirmed on initial sample or it is not possible to repeat testing using initial sample, the data in the DILI checklist is collected and followed up simultaneously to meet the following timelines (or as quickly as possible, if the timelines cannot be met):

- Reflex testing from initial blood sample within 24 hours upon laboratory hepatic injury alert / notification, including (if appropriate specimen is available):
  - Repeat of AST, ALT, bilirubin (with fractionation to total and direct)
  - Creatinine kinase
  - Acetaminophen level
  - Lactate dehydrogenase
  - Haptoglobin
  - Complete blood count and cell morphology
  - Reticulocyte count
  - Alkaline Phosphatase
- DILI Kit assessment (new blood sample) within 48 hours upon laboratory hepatic injury alert / notification
- Abdominal ultrasound: within 48 hours upon laboratory hepatic injury alert / notification
- The following part of the DILI checklist is collected within 48 hours upon receipt of the laboratory hepatic injury alert / notification:
  - Alcohol consumption
  - Medical history / concomitant diagnoses
  - Complete physical examination
  - Concomitant therapy/supplements

- Complete the following laboratory tests as detailed in the DILI checklist provided in the ISF:
    - *Clinical chemistry*
      alkaline phosphatase, cholinesterase (serum)*, albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin*, amylase, lipase, fasting glucose, cholesterol, triglycerides;
    - *Serology*
      Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM)*, varicella (IgG, IgM)*, parvovirus (IgG, IgM)*;
    - *Hormones, tumour marker*
      TSH*;
    - *Haematology*
      Thrombocytes, eosinophils.

*If clinically indicated (e.g. immunocompromised patients)

The results of these tests must be reported to BI as soon as possible. In case the etiology of the abnormal liver tests results is not identified based on the imaging (e.g. biliary tract, pancreatic, or intrahepatic pathology), the “DILI checklist” must be completed. Details of the “DILI checklist” are provided in the ISF. The following assessments need to be performed in order to complete the “DILI checklist” and results will be reported via the eCRF:

Long term follow-up:

- Initiate close observation of patients by repeat testing of ALT, AST, and bilirubin (with fractionation to total and direct) at least weekly until the laboratory ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and GCP and reported via the eCRF.

10.6 CREATININE CLEARANCE

Creatinine clearance should be calculated per institutional standard.

The following formula may be used for estimated creatinine clearance rate (eCCR) using Cockcroft-Gault formula. The calculations and results must be filed in the patient's chart.

When serum creatinine is measured in mg/dl;

$$eC_{CR} \cong \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot [0.85 \; if \; Female]}{72 \cdot \text{Serum Creatinine}(\text{in mg/dl})}$$

When serum creatinine is measured in µmol/l;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot \text{Constant}}{\text{Serum Creatinine}(\text{in µmol/l})}$$

Where *Constant* ≈*1.23* for men and *1.04* for women.

10.7 ECOG PERFORMANCE STATUS

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

* As published in Am. J. Clin. Oncol. (R01-0787).

10.8 P-GLYCOPROTEIN INHIBITORS AND INDUCERS

Examples of P-gp modulators that can be considered as potent inhibitors and/or potent inducers of the P-gp (P-gp is also known as MDR1) are listed in Table 10.8: 1.

Table 10.8: 1 List of potent inhibitors and inducers of P-glycoprotein (MDR1)

Inhibitors	Inducers
Amiodarone	Carbamazepine
Azithromycin	Phenytoin
Captopril	Rifampicin
Carvedilol	St John's wort
Clarithromycin	Phenobarbital salt
Conivaptan	Tipranavir
Cyclosporine	Ritonavir
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir	
Nelfinavir	
Ritonavir	
Quinidine	
Ranolazine	
Saquinavir	
Tacrolimus	
Ticagrelor	
Verapamil	

As the information on potent inhibitors and inducers of P-gp may evolve, it is important for the investigator to assess such status on concomitant therapies and in case of questions contact sponsor/sponsor representative.

10.9 BAYESIAN LOGISTIC REGRESSION MODEL WITH OVERDOSE CONTROL FOR DOSE CONFIRMATION

A Bayesian logistic regression model (BLRM) with overdose control that will be fitted to binary toxicity outcomes will be used to guide the dose confirmation part in this study. After 12 patients completed at least one cycle of treatment, the prior distributions will be updated through Gibbs sampling procedures with the accumulated DLT data from the first treatment cycle. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of the dose confirmation, the toxicity probability at each dose level will be calculated to determine an estimate of the RP2D. Posterior probabilities for the rate of DLT will be summarised from BLRM. Confirmation of the RP2D by the SMC will be based on these probabilities as well as on the review of other safety and laboratory data.

The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the RP2D under various dose-toxicity relationships through computer simulation. These results are summarised in Table 10.9.2: 2. Recommendations by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios to show how it facilitates the decision making process by the SMC (see Table 10.9.3: 1).

Please note that RStudio Version 0.99.484 and R version 3.2.2 were used for the computations shown in the subsequent parts of this appendix.

10.9.1 Definition of the model and description of the prior derivation

As described in Sections 1.4 and 3.1, the dose confirmation part will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R13-4806, R13-4803).

This logistic regression model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of afatinib as monotherapy, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of pembrolizumab as monotherapy, respectively. A logistic regression is used to model the dose-toxicity relationship for each of these drugs individually:

- Afatinib: $\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$
- Pembrolizumab: $\text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

Here, the doses $d_1^* = 40$ mg and $d_2^* = 200$ mg represent the reference doses for afatinib and pembrolizumab, respectively.

Assuming no toxicity interaction between the two compounds, the probability of a DLT when giving the combination dose d_1, d_2 is obtained as

- $\pi^0_{12,d1,d2} = \pi_{1,d1} + \pi_{2,d2} - \pi_{1,d1}\pi_{2,d2}$

with corresponding odds

- $\text{odds}(\pi^0_{12,d1,d2}) = \pi^0_{12,d1,d2} / (1 - \pi^0_{12,d1,d2})$.

In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction

between afatinib and pembrolizumab, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced in the model by the following definition:

- $odds(\pi_{12,d1,d2}) = odds(\pi^0_{12,d1,d2}) \exp(\eta\ d_1/d_1^*\ d_2/d_2^*)$

  and $\pi_{12,d1,d2}$ is used in the likelihood
- $r_{d1,d2} \sim Binomial(n_{d1,d2},\pi_{12,d1,d2})$

where $r_{d1,d2}$ denotes the random variable describing the observed number of DLTs in $n_{d1,d2}$ patients at the dose combination d_1, d_2.

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified.

The prior distributions for θ_k will be specified as a mixture of two bivariate normal distributions,

$f(\theta_k) = a_{1,k}\ f_1(\theta_k) + a_{2,k}\ f_2(\theta_k)$

with

$a_{1,k}$, $a_{2,k}$ the prior mixture weights ($a_{1,k} + a_{2,k} = 1$), k = 1,2 and

$f_i(\theta_k) = MVN(\mu_{ik}, \sum_{ik})$ a bivariate normal distribution with mean vector μ_{ik} and covariance matrix $\sum_{ik}$ where

$$\Sigma_{ik} = \begin{pmatrix} \sigma^2_{ik,11} & \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} \\ \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} & \sigma^2_{ik,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

A weakly informative normal prior distribution will be used for η.

The estimated probability of DLT $\pi_{12,d1,d2}$ at each dose combination d_1, d_2 from the model will be summarised using the following intervals:

- Under dosing: [0.00, 0.16)
- Targeted toxicity: [0.16, 0.33)
- Over dosing: [0.33, 1.00]

The BLRM recommended dose combination is the combination with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the dose combinations fulfilling the overdose control. It should be unlikely (<25% posterior probability) that the DLT rate at the dose combination will exceed 0.33.

For the dose confirmation part, the RP2D may be considered reached if the posterior probability of the true DLT rate in the target interval [0.16 – 0.33) is above 0.50.

Prior toxicity information on afatinib was taken from 1200.2, 1200.3 and 1200.4 to define the prior distribution of this model, using the meta-analytic predictive approach (U07-3128-02 and U08-1023-02).For pembrolizumab it was not possible to utilise information from the dose-finding studies as body weight dependent dosing regiments were originally investigated. For this part of the prior derivation process a minimally informative prior is utilised, combining high-tox, low-tox and expected average tox probabilities.

Prior derivation

For summaries of the data from other BI trials, see Table 10.9.1: 1 below.

Table 10.9.1: 1 Summary of data from trials 1200.2, 1200.3, and 1200.4 used for the prior derivation for afatinib

Dose (mg)	1200.2		1200.3		1200.4	
	# Patients treated	# DLT events	# Patients treated	# DLT events	# Patients treated	# DLT events
10	3	0	3	0	5	0
20	6	0	4	0	3	0
30	-----	-----	7	1	-----	-----
40	8	1	26	1	19	1
50	-----	-----	13	1	-----	-----
55	20	7	-----	-----	-----	-----
60	-----	-----	-----	-----	3	2
65	6	3	-----	-----	-----	-----

The following steps were used to derive the prior distributions for all parameters:

- θ_1:
  - The meta-analytic-predictive prior was derived using the information in Table 10.9.1:1, allowing for substantial between-trial heterogeneity
  - This mixture component was assigned 90% mixture weight. A second, weakly-informative component was added with 10% mixture weight
- θ_2:
  - A weakly informative prior was derived reflecting the a priori assumption that the median DLT rates at the dose of 150 mg would be equal to 1% and 200 mg 3-weekly pembrolizumab would equal to 2 %. This yields $\mu_1 = (-3.892 , 0.894)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 2$ and $\rho_1 = 0$, respectively. The prior weight φ_1 for the first component was chosen as 0.9.

- A high-toxicity weakly informative prior was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rates at the dose of 150 mg would be equal to 5% and 200 mg would equal to 15%. These assumptions yield $\mu_2 = (0.05, 0.15)$. The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 2$ and $\rho_2 = 0$, respectively. The prior weight φ_2 for the second component was chosen as 0.05.
- A low-toxicity weakly informative prior was derived reflecting the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rates at the starting dose of 150 mg would be equal to 0.1% and 200 mg would equal to 0.2. These assumptions yield $\mu_3 = (0.001, 0.002)$. The standard deviations and correlations were set to $\sigma_{3,11} = 2$, $\sigma_{3,22} = 2$ and $\rho_3 = 0$, respectively. The prior weight φ_3 for the third component was chosen as 0.05.

- η:
  - Based on the a priori assumption of no interaction between the two compounds, a normal distribution with mean 0 and standard deviation 0.707 was chosen. At the starting dose combination, the corresponding 95% prior interval covers an up to 4-fold increase (or decrease) in the odds of a DLT over no interaction.

The corresponding prior distribution parameters can be found in Table 10.9.1: 2 probabilities of a DLT at different dose combinations of afatinib and pembrolizumab, and the corresponding probability of under-dosing, targeted dosing and overdosing based on the computed prior are shown in Table 10.9.1: 3. Based on the aforementiend table, a starting dose of 40 mg daily afatinib in combination with 200 mg of 3 weekly pembrolizumab fulfills the overdose criterion and is therefore a suitable starting dose.

Table 10.9.1: 2 Prior distribution parameters for the combination of afatinib and pembrolizumab

Parameter	Means, standard deviations, correlation	Mixture weight
Component 1: log(α1),log(β1)	(-2.197, 0.967), (1.201, 0.794), -0.077	0.9
Component 2: log(α1), log(β1)	(-2.2, 1), (1.5, 1), 0	0.1
Component 1: log(α2), log(β2)	(-3.892 , 0.894), (2, 2), 0	0.9
Component 2: log(α2), log(β2)	(-1.735, 1.436), (2, 2), 0	0.05
Component 3: log(α2), log(β2)	(-6.213, 0.881), (2, 2), 0	0.05
η	0, 0.707, NA	NA

Table 10.9.1: 3 Prior probabilities of true DLT rates with 200 mg of 3-weekly pembrolizumab with 20, 30 or 40 mg of daily afatinib

Afatinib dose mg	Probability of true DLT rate in					Quantiles		
	[0,0.16]	[0.16,0.33]	[0.33,1]	Mean	Standard Deviation	2.5%	50%	97.5%
20mg	0.767	0.138	0.095	0.120	0.159	0.002	0.058	0.622
30mg	0.668	0.191	0.141	0.160	0.177	0.006	0.094	0.686
40mg	0.499	0.256	0.245	0.229	0.206	0.014	0.160	0.779

Study 1200.237, an investigator initiated study, is already investigating the dose combination of 40 mg daily afatinib and 200 mg of 3-weekly pembrolizumab, and it was seen as valuable to incorporate the prior information based on the previously described prior derivation with real data of the combination of these two compounds. The relevant information from 1200.237 can be found in Table 10.9.1: 4. The aforementioned prior was combined with the data from 1200.237 and the predicted prior probabilities of DLTs occurring within this study were re-computed. The results are shown in Table 10.9.1: 5.

Table 10.9.1: 4 Summary of data from trial 1200.237

Dose (mg)	1200.237	
	# Patients treated	# DLT events
40 mg daily afatinib + 200 mg 3-weekly pembrolizumab	4	0

Table 10.9.1: 5 Prior probabilities of true DLT rates with 200 mg of 3-weekly pembrolizumab with 20, 30 or 40 mg of daily afatinib after the incorporation of data from 1200.237

Afatinib dose mg	Probability of true DLT rate in					Quantiles		
	[0,0.16]	[0.16,0.33]	[0.33,1]	Mean	Standard Deviation	2.5%	50%	97.5%
20mg	0.936	0.056	0.008	0.053	0.064	0.002	0.031	0.236
30mg	0.895	0.093	0.012	0.071	0.072	0.004	0.048	0.269
40mg	0.776	0.186	0.038	0.110	0.096	0.010	0.082	0.369

Based on the above table, a starting dose of 40 mg daily afatinib in combination with 200 mg of 3 weekly pembrolizumab can be seen as adequately safe to treat patients in this study.

Current available information obtained from the study 1200.237 at the time of dose escalation will be incorporated in the calculation of the posterior.

10.9.2 Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.9.2: 1 describes 4 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1: aligned with prior means
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: low-toxicity followed by high-toxicity

Table 10.9.2: 1 Assumed true dose-toxicity scenarios

Scenario		Dose combination (afatinib/pembrolizumab)		
		20/200	30/200	40/200
Scenario 1	P(DLT)	0.051	0.068	0.103
Scenario 2		0.10	0.15	0.24
Scenario 3		0.03	0.05	0.07
Scenario 4		0.03	0.10	0.26

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 12 patients. It was then assessed how often a dose was declared as RP2D with true DLT rate in the under-, targeted, or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.9.2: 2 below.

Table 10.9.2: 2 Simulated operating characteristics

Scenario	% of trials confirming RP2D with true DLT rate in				# Patients	# DLTs
	Underdose	Target Dose	Overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
1	48.2	51.3	0.0	0.5	18.69 (12-30)	2.47 (0-7)
2	10.0	85.1	2.9	0.3	17.17 (6-30)	4.13 (1-11)
3	38.8	60.5	0.0	1.2	19.45 (12-30)	2.31 (0-7)
4	12.6	83.0	2.6	0.4	17.41 (6-30)	4.28 (1-10)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, almost all of the simulated trials have found a RP2D. Most of those trials declared the RP2D with true toxicity rate in the target interval; however, many declared a dose with true toxicity rate in the underdose interval. Very few trials stopped prematurely without an RP2D, indicating that by chance it may be seen that the dose combination can also be perceived as being too toxic.

Scenario 2 (high-toxicity scenario) illustrates that even with a doubling of the true underlying dose-toxicity rate it would be possible to declare an RP2D at the target dose level in over 85% of the cases. Stopping in the underdose interval was observed in 10% of cases, and in the overdose interval in less than 3% of cases. A few simulated trials have been stopped before declaring a RP2D, but the number is still low and expected behaviour for a high-toxicity scenario.

In scenario 3 (low-toxicity scenario) none of trials declared a RP2D with true DLT rate in the overdose interval. Furthermore, around 39% of trials that declared a RP2D with true DLT rate in the underdose interval were simulated in this scenario. Most trials that have found a RP2D declared this RP2D with true DLT rate in the target interval (60.5%).

Scenario 4, a mixture of the high toxicity and the low toxicity scenario, shows characteristics of both of these.

The mean patient numbers range from 17.17 patients (Scenario 2) to 19.45 patients (Scenario 3) and the maximum number of patients was 30. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

10.9.3 Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.9.3: 1. These scenarios reflect potential on-study data constellations and related potential de-escalation of afatinib as suggested by the

model. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of underdosing, target dosing and overdosing are shown.

Scenarios 1 to 5 represent the situation at the first pre-planned formal evaluation after 12 patients have been treated with the starting dose combination of 40 mg daily afatinib and 200 mg 3-weekly pembrolizumab. It can be seen that up to 4 out of 12 treated patients experiencing a DLT would lead to the acceptance that this starting dose is an adequate RP2D. With 5 or 6 patients with a DLT in the first treatment cycle the model would suggest to reduce the dose to 30 mg daily afatinib, as 40 mg are too toxic. With 7 patients experiencing a DLT in the aforementioned time interval, the model would suggest that even 30 mg afatinib is too toxic and any patient exposed to the combination should receive 20 mg of afatinib. With 8 or more DLTs, any afatinib dose is considered to be too toxic and no new patient should be exposed to the combination of afatinib and pembrolizumab.

Scenarios 6 to 12 show the cases where 5 DLTs were observed in the first 12 patients in the first treatment cycle and the second run in cohort on 30 mg is introduced. If 0 or 1 DLTs are observed in these 12 patients, then the model would suggest that the afatinib dose could potentially again increase; however. Observing 2 to 4 DLTs would confirm that the de-escalation was an adequate step and could be seen as RP2D. If 5 DLTs would be recorded in the first treatment cycle in this group of 12 patients, then another dose reduction to 20 mg afatinib would be required. With 6 or more DLTs any afatinib dose in combination with pembrolizumab would be determined as being too toxic to expose patients to.

Scenarios 13 to 18 show the cases where 6 DLTs were observed in the first 12 patients in the first treatment cycle and the second run in cohort on 30 mg is introduced. If 0 to 4 DLTs are observed in these 12 patients, then the model would suggest that the selected afatinib dose is adequate and could be seen as RP2D. If 4 DLTs would be recorded in the first treatment cycle in this group of 12 patients, then another dose reduction to 20 mg afatinib would be required. With 5 or more DLTs any afatinib dose in combination with pembrolizumab would be determined as being too toxic to expose patients to.

Table 10.9.3: 1 Hypothetical Data Scenarios

Scenario	Current Dose Combination (mg/mg)	# Patients	# DLT	Current Dose Combination P(OD)[1]	Next Recommended Dose Combination (mg/mg)	Next Dose Combination		
						P(UD)[2]	P(TD)[3]	P(OD)[1]
1	40/200	12	4	0.160	40/200	0.229	0.661	0.160
2	40/200	12	5	0.321	30/200	0.428	0.473	0.099
3	40/200	12	6	0.516	30/200	0.315	0.499	0.186
4	40/200	12	7	0.715	20/200	0.464	0.356	0.181
5	40/200	12	8	0.849	-----	-----	-----	-----
6	40/200 30/200	12 12	5 0	0.002	40/200	0.225	0.644	0.130

Scenario	Current Dose Combination (mg/mg)	# Patients	# DLT	Current Dose Combination P(OD)[1]	Next Recommended Dose Combination (mg/mg)	Next Dose Combination		
						P(UD)[2]	P(TD)[3]	P(OD)[1]
7	40/200 30/200	12 12	5 1	0.010	40/200	0.142	0.677	0.180
8	40/200 30/200	12 12	5 2	0.039	30/200	0.425	0.536	0.039
9	40/200 30/200	12 12	5 3	0.087	30/200	0.244	0.669	0.087
10	40/200 30/200	12 12	5 4	0.191	30/200	0.115	0.694	0.191
11	40/200 30/200	12 12	5 5	0.322	20/200	0.249	0.545	0.206
12	40/200 30/200	12 12	5 6	0.489	-----	-----	-----	-----
13	40/200 30/200	12 12	6 0	0.005	30/200	0.799	0.197	0.005
14	40/200 30/200	12 12	6 1	0.025	30/200	0.560	0.415	0.025
15	40/200 30/200	12 12	6 2	0.067	30/200	0.326	0.607	0.067
16	40/200 30/200	12 12	6 3	0.152	30/200	0.170	0.678	0.152
17	40/200 30/200	12 12	6 4	0.280	20/200	0.345	0.505	0.151
18	40/200 30/200	12 12	6 5	0.451	-----	-----	-----	-----

[1] Probability of Overdosing

[2] Probability of Underdosing

[3] Probability of Target Dosing

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		12 Mar 2019
EudraCT number **EU number**		2016-005042-37
BI Trial number		1200.283
BI Investigational Product(s)		Afatinib + pembrolizumab
Title of protocol		LUX-Lung IO: A phase II, open label, non-randomised study of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous cell carcinoma of the lung
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Title page
Description of change		Administrative changes for TCM, version and date
Rationale for change		To reflect the change in TCM for the study, version number and date of new version
Section to be changed		Flowchart
Description of change		Timeline for Screening Period; remove FUPfor PD and OS; thyroid testing; AE reporting period for pembrolizumab;
Rationale for change		Allow patients to be randomised at the screening visit if all procedures are completed to avoid unnecessary visit. To clarify that thyroid testing after discontinuation pembrolizumab is only needed if clinically indicated. To clarify that AEs are to be collected up to 90 days after the last dose of pembrolizumab. With the early termination of the study patients are no longer followed for PD and OS and blood samples for biomarkers are no longer needed at time pf PD. With the early termination of the study tumour assessment is done per standard of care.
Section to be changed		Section 2.2.1

Description of change		There will be no assessment of biomarkers in blood samples.
Rationale for change		Because of the early termination of the study this assessment is no longer needed.
Section to be changed		Section 3.1
Description of change		SMC recommendation to stop the trial and not open the Main part of the study
Rationale for change		SMC determined that the benefit risk of the combination of pembrolizumab and afatinib was not favourable.
Section to be changed		Section 3.3.4 and 3.3.4.1
Description of change		Add that patients will be discontinued from the trial treatment after completing 35 cycles with pembrolizumab and/or afatinib. Patients will not be followed up for disease progression or overall survival after discontinuation from trial treatment.
Rationale for change		For clarity and consistency with other sections of the protocol. Cancellation of patient follow-up for PD and OS.
Section to be changed		Table 4.1.4.2.1:1
Description of change		Guidance on dose modification in patients with • Liver metastasis at baseline who experience AST or ALT elevation • Myocarditis • Other immune-related AEs of grade 3
Rationale for change		To be consistent with dose modification described in the SmPc for pembrolizumab
Section to be changed		Section 4.1.4.2.2
Description of change		New section
Rationale for change		To provide guidance on dose interruption for pembrolizumab for reasons other than treatment related AE
Section to be changed		Section 4.2.1
Description of change		Clarification and guidance on supportive care measure for treatment with pembrolizumab
Rationale for change		It was missing for pembrolizumab.
Section to be changed		Section 4.2.2.1
Description of change		• Delete “oral” in “typhoid oral vaccine • Add that systemic glucocorticoids can be used to treat adverse reactions to afatinib
Rationale for change		• To clarify that any type of typhoid vaccines are excluded • To clarify that glucocorticoids can be used to treat adverse reactions for afatinib
Section to be changed		Table 4.2.3.3:1

Description of change		Add that treatment with afatinib should be interrupted for Grade 2 diarrhea if it is intolerable for patients
Rationale for change		To clarify that treatment interruption of grade 2 diarrhea is also based on patient decision
Section to be changed		Section 4.2.3.10
Description of change		Add that pembrolizumab may cause severe or life threatening infusion reactions with reference to the guidelines in the protocol.
Rationale for change		Clarification on management of infusion reaction with pembrolizumab
Section to be changed		Table 4.2.3.10:1
Description of change		• Editorial changes • Clarification on when to use epinephrine • Reference to CTCAE guidelines
Rationale for change		Clarification on management of infusion reaction with pembrolizumab
Section to be changed		Sections 5.1.1 and 5.1.2
Description of change		Tumour assessment will be done per local standard of care and will not have to follow RECIST 1.1
Rationale for change		Clarification of expectation with the early termination of the study.
Section to be changed		Section 5.2.5.2
Description of change		ECOG evaluation is no longer required
Rationale for change		Clarification of expectation with the early termination of the study.

Section to be changed		Section 5.1.1
Description of change		• Add clarification as to why the same imaging technique should be used. • Clarify that imaging manual will be provided in case of retrospective review • Guidance on imaging after progressive disease per irRECIST
Rationale for change		Clarification on imaging during the trial
Section to be changed		Section 5.1.2
Description of change		• Clarification on imaging requirement for patients who have PD according to RECIST but are clinically stable. • Definition of clinical stability in the context of the study
Rationale for change		Added clarification on imaging requirement for PD according to irRECIST
Section to be changed		Table 5.1.2:1
Description of change		Clarification on imaging and treatment after first radiologic evidence of PD
Rationale for change		Added clarification on imaging during the trial
Section to be changed		Section 5.2.3
Description of change		Add that thyroid function testing is done only while on treatment with pembrolizumab
Rationale for change		Clarification on thyroid testing during the trial
Section to be changed		Section 5.2.5.1
Description of change		Added “possibly, probably and definitely” to related toxicities for assessing DLTs.
Rationale for change		To clarify the relatedness of toxicities that will be used to determine DLTs
Section to be changed		Table 5.2.5.1:1
Description of change		Delay in initiating dosing in Cycle 2 to include pembrolizumab and afatinib
Rationale for change		To clarify that delay in dosing applies to both trial drugs i.e afatinib and pembrolizumab.
Section to be changed		Section 5.2.6.1
Description of change		AESIs-hepatic injury • Guidance on assessment following elevation of liver enzymes
Rationale for change		Clarification on the assessment and evaluation of elevated liver enzymes during the conduct of the trial
Section to be changed		Section 5.2.6.2
Description of change		AE reporting period for pembrolizumab and afatinib AESIs, AEs and SAEs are not collected after the end of the REP

Rationale for change		Clarify that for pembrolizumab duration of (S)AEs collection and reporting after end of REP is 90 days
Section to be changed		Section 5.3.2
Description of change		Correction of the blood volume for PK assessment
Rationale for change		Editorial error
Section to be changed		Section 5.4.2
Description of change		There will be no assessment of biomarkers in blood samples.
Rationale for change		Because of the early termination of the study, this assessment is no longer needed.
Section to be changed		Section 6.2.3
Description of change		Separate EOR visit from FUP visit
Rationale for change		To clarify that FUP visit and EOR visit are independent
Section to be changed		Section 8.6
Description of change		Change in the definition of "The end of the trial"
Rationale for change		In line with the early termination of the study patients will no longer be followed for 24 months
Section to be changed		Section 10.1
Description of change		PK sampling to be done shortly before trial drug administration rather than fixed time of 5 min prior to dosing
Rationale for change		Provide flexibility in the timing of PK sampling.
Section to be changed		Section 10.4
Description of change		Clarification on imaging after evidence of radiological PD.
Rationale for change		To be consistent with changes in Sections 5.1.1 and 5.1.2.
Section to be changed		Section 10.9.1
Description of change		• Include 150 mg in prior derivation for afatinib • Data from 1200-237 will be incorporated in calculation of the posterior
Rationale for change		• To include in the BLRM the 2 doses tested in the trial i.e 150 mg and 200 mg • Clarify how data from 1200.237will be included in statistical calculation

11.2 GLOBAL AMENDMENT 2

Date of amendment		11 Apr 2019
EudraCT number **EU number**		2016-005042-37
BI Trial number		1200.283
BI Investigational Product(s)		Afatinib + pembrolizumab
Title of protocol		LUX-Lung IO: A phase II, open label, non-randomised study of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous cell carcinoma of the lung
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Section 3.1
Description of change		Updated language for the SMC recommendation to stop the trial and not open the Main part of the study.
Rationale for change		Correction to add text not previously incorporated in Version 2

APPROVAL / SIGNATURE PAGE

Document Number: c13055147 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: LUX-Lung IO: A phase II, open label, non-randomised study of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous cell carcinoma of the lung

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		12 Apr 2019 16:23 CEST
Approval-Clinical Trial Leader		12 Apr 2019 16:34 CEST
Approval-Biostatistics		12 Apr 2019 16:47 CEST
Approval-Therapeutic Area		15 Apr 2019 08:57 CEST
Verification-Paper Signature Completion		15 Apr 2019 19:57 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed