Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c03352377-02
BI Study Number:	1199.223
BI Investigational Product(s):	Vargatef® (nintedanib)
Title:	A non-interventional biomarker study in patients with Non-Small Cell Lung Cancer (NSCLC) of adenocarcinoma tumour histology eligible for treatment with Vargatef® according to the approved label.
Protocol version identifier:	02
Date of last version of protocol:	09 May 2019
PASS:	No
EU PAS register number:	ENCEPP/SDPP/11885
Active substance:	Nintedanib Antineoplastic agents, protein kinase inhibitors ATC code: L01XE31
Medicinal product:	Vargatef®,100 mg and 150 mg soft capsules
Product reference:	EU/1/14/954/001-004
Procedure number:	EMA/H/C/002569
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH
Joint PASS:	No
Research question and objectives:	To explore whether genetic/genomic markers (alone or combined with clinical covariates) could be used to predict overall survival (OS) in NSCLC patients eligible for treatment with Vargatef® according to the approved label
Countries of study:	Multi-center study conducted in 13 countries: Austria, Belgium, Denmark, Germany, Greece, Hungary, Italy, Lithuania,

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	Luxembourg, Netherlands, Spain, Sweden and UK.
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Date:	09 May 2019
Page 1 of 43	

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1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Abl1	ABL proto-oncogene 1, non-receptor tyrosine kinase
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
BI	Boehringer Ingelheim
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CA	Competent Authority
CDR	Clinical Data Repository
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTNNB1	Catenin (cadherin-associated protein), beta 1, 88kDa
CTR	Clinical Trial Report
DDR1&2	Discoidin Domain Receptor tyrosine kinase 1 and 2
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group performance score
EDTA	Etylen-Diamin-Tetra-Acetat
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EU	European Union
EU PAS	European Union Post-Authorization Studies
FDA	US Food and Drug Administration
FPE	Fixed Paraffin Embedded
FGFR	Fibroblast Growth Factor Receptor
Flt3	Fms-related tyrosine kinase 3
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practice
HER2	erb-b2 receptor tyrosine kinase 2 (ERBB2)
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
Kit	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
KRAS	Kirsten rat sarcoma viral oncogene homolog
Lck	LCK proto-oncogene, Src family tyrosine kinase
LDH	Lactade Dehydrogenase
MedDRA	Medical Dictionary for Drug Regulatory Activities
Melk	Maternal embryonic leucine zipper kinase
ml	milliliter

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NIS	Non-Interventional Study
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
NSCLC	Non-Small Cell Lung Cancer
OPU	Operative Unit
OS	Overall Survival
PDGFR	Platelet Derived Growth Factor Receptor
PD-L1	Programmed death-ligand 1
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria In Solid Tumours
Ret	Ret proto-oncogene
RNA	Ribonucleic acid
ROS	Proto-oncogene 1 , receptor tyrosine kinase
SAE	Serious Adverse Event
SCLC	Small-Cell Lung Cancer
SADR	Serious Adverse Drug Reaction
SEAP	Statistical and Epidemiological Analysis Plan
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
Src	SRC proto-oncogene, non-receptor tyrosine kinase
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMM	Team Member Medicine
TrkA (NTRK1)	Neurotrophic Tyrosine Kinase, receptor, type 1
TrkC (NTRK3)	Neurotrophic Tyrosine Kinase, receptor, type 3
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

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3. RESPONSIBLE PARTIES

Boehringer Ingelheim (BI) has appointed a Clinical Trial Leader (CTL), responsible for coordinating all required activities, in order to

- manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs),
- direct the study team in the preparation, conduct, and reporting of the study,
- order the materials as needed for the study,
- ensure appropriate training and information of Clinical Trial Managers (CTMs), Clinical Research Associate (CRAs), and Physicians of participating countries.

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

The organization of the study in the participating countries will be done by the respective local BI-operative unit (OPU) or by a Contract Research Organization (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study. In each local BI OPU participating in this study, a CTM will be appointed responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU. On-site monitoring will be performed by BI or a CRO appointed by BI.

Assessments of pharmacogenomics and biomarkers is planned to be performed centrally. All samples will be sent by the participating sites to a vendor and forwarded subsequently to the central laboratory for analysis.

An Investigator Site File (ISF) containing all relevant study related documentation will be maintained according to local regulations and BI SOPs at each study site. A copy of the ISF documents will also be kept as an electronic Trial Master File (TMF) at BI according to BI SOPs. Documents related to participating physicians and other important participants, especially their curricula vitae, will be filed in the TMF.

The coordinating physicians who will sign the non-interventional study report of this study have been appointed by BI. The coordinating physician has experience in this type of studies.

Coordinating physician: Co- Coordinating physician:

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Vargatef®			
Name of active ingredient: Nintedanib, Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE31			
Protocol date: 07 October 2015	**Study number:** 1199.223	**Version/Revision:** 02/01	**Version/Revision date:** 09 May 2019
Title of study:	A non-interventional biomarker study in patients with NSCLC of adenocarcinoma tumour histology eligible for treatment with Vargatef® according to the approved label.		
Rationale and background:	At present there are no validated predictive tumour- or serum-derived biomarkers available guiding the usage of anti-angiogenic therapies in NSCLC. The objective of this non-interventional study (NIS) is to explore predictive genetic/genomic markers (alone or combined with clinical covariates) in NSCLC patients eligible for treatment with Vargatef®. The analyses in this study are exploratory in nature and considered to be hypothesis generating. The results from these investigations may help to expand our understanding of the disease and the response to Vargatef®.		
Research question and objectives:	To explore whether genetic/genomic markers (alone or combined with clinical covariates) could be used to predict OS in NSCLC patients treated with Vargatef® according to the approved label.		
Study design:	Non-interventional, multi-country, multi-site study based on newly collected data in patients that are assigned to receive Vargatef® as part of the routine treatment according to the approved label for the first time (new users design). Patients will be followed up until death, lost to follow-up, withdrawal of consent, or until required number of OS events has occurred, whichever occurs first.		
Population:	Patients that are assigned to treatment with Vargatef® as part of the routine treatment according to the approved label are eligible for participation in the study.		

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Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Vargatef®			
Name of active ingredient: Nintedanib, Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE31			
Protocol date: 07 October 2015	**Study number:** 1199.223	**Version/Revision:** 02/01	**Version/Revision date:** 09 May 2019
	It is intended that about 100 sites with oncologists/pulmonologists at hospitals mainly based in Europe will participate. An average of 0.2 patients/months/site is expected. If patient recruitment takes longer than expected, the number of participating sites and the number of included patients per site may be increased.		
Variables:	Primary outcome: OS in relation to exploratory biomarker assessment, including gene-expressions and genomic alterations.		
Data sources:	NIS based on new data collection (NISnd).		
Study size:	At least 300 evaluable patients. In order to account for possible non-evaluable patients up to 375 can be enrolled.		
Data analysis:	Univariate and multivariate prediction models will be used to identify gene expressions and tumour genomic alterations to predict OS in patients with NSCLC treated with Vargatef®.		
Milestones:	First included patient 14 March-2016. Final report of study results expected in August-2020		

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5. AMENDMENTS AND UPDATES

Global Amendment 1

Number	Section of study protocol	Amendment or update	reason
1	Title page	EU PAS register number	Not assigned before finalization of the protocol
2	Title page	Countries of study	Updated with the participating countries
3	P.2	Author	Name and address of the author updated
4	Section 2	List of abbreviations	Updated with missing (PD-L1) and updated (TCM→CTL and CML→CTM) abbreviations throughout the protocol
5	Section 4	Milestones	Updated with actual date for first included patient and revised planned expected date of the final study report
6	Section 6	Milestones	Updated with actual and planned dates
7	Section 9.3	Variables collected at Baseline visit	Corrections of percentage of PD-L1 positive myeloid cells to PD-L1 positive immune cells
8	Section 9.3	Variables collected at Follow-up visits	Added to collect: Best response after Vargatef® and docetaxel treatment (according to RECIST 1.1(R09-262) if possible).

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6. MILESTONES

Milestone	Planned Date
Registration in the European Union (EU) Post-Authorization Studies (PAS) register	22-Jan-2016
Start of data collection	14 Mar 2016
End of data collection	30-Aug-2019
Final report of study results:	30-Aug-2020

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7. RATIONALE AND BACKGROUND

Lung cancer is the most common cancer worldwide. In 2008, 1.6 million people were newly diagnosed with lung cancer worldwide, and 1.4 million deaths were caused by lung cancer i.e., 18% of the overall cancer mortality, being so the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women (R12-1150). Histologically, a distinction is drawn between NSCLC and small-cell lung cancer (SCLC), based on the differences in terms of biological behaviour, prognosis and treatment options. About 80% - 85% of lung cancers involve NSCLCs, which are divided into three basic histological subgroups: adenocarcinoma, squamous cell carcinoma and large cell carcinoma (R08-5110). The majority of patients with lung cancer are diagnosed after the disease has progressed to an advanced stage. The prognosis for the majority of patients with advanced stage disease has not changed significantly in the past decade. With an overall 5-year survival rate of 9 to 13%, the treatment of NSCLC remains a major clinical challenge (R11-0052). Although considerable progress has been made in understanding the underlying biologic and genetic basis of cancer which has resulted in the development of more effective and targeted treatment strategies.

The aim of treatment of NSCLC is the reduction of tumour -related symptoms and the prolongation of survival time.

Vargatef® is an oral small molecule triple receptor tyrosine kinase inhibitor that potently blocks vascular endothelial growth factor-receptor (VEGFR) 1-3, fibroblast growth factor/receptor (FGFR) 1 and 3, as well as platelet derived growth factor- receptor (PDGFR), beside Ret proto-oncogene (ret), Src and Fms-related tyrosine kinase 3 (FLT3) in low nanomolar concentrations.

Vargatef® was approved in the EU on 12 November 2014 by the European Medicines Agency (EMA) for the following indication: Vargatef® is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy (c01632700-18).

The approval of Vargatef® was based on the survival benefit observed in the LUME-Lung 1 study. LUME-Lung 1 was a double-blind, randomised, phase III study to evaluate the efficacy and safety of Vargatef® in combination with docetaxel in patients with locally advanced/metastatic or recurrent NSCLC following failure of first-line chemotherapy versus placebo plus docetaxel. The median OS of NSCLC patients with adenocarcinoma was prolonged by combination therapy of Vargatef®+ docetaxel versus docetaxel monotherapy from 10.3 to 12.6 months (Hazard Ratio (HR) 0.83; p = 0.0359). In addition, it was shown in a prespecified analysis that patients with progression during or shortly after first-line therapy (within 9 months after the start of first line chemotherapy) benefited with a median OS prolongation from 7.9 to 10.9 months (HR 0.75; p = 0.0073). A further exploratory evaluation was performed for patients who progressed directly on first-line therapy. In these patients, OS was also prolonged from 6.3 to 9.8 months (HR 0.62; p = 0.0246).
The most common adverse events (AEs) to be observed in the LUME-Lung 1 study were gastrointestinal adverse effects as well as reversible increases in liver enzymes, which were

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usually well controlled by supportive measures or dose reduction. In terms of the class-specific adverse effects known for antiangiogenic therapies (hypertension, haemorrhage or thrombosis of grade 3 severity), no differences were found between the two treatment arms (P14-00479).

At present there are no approved predictive tumour- or serum-derived biomarkers guiding usage of anti-angiogenic therapies in patients with adenocarcinoma of NSCLC. Consequently, EMA requested BI to search for potential predictive biomarkers in NSCLC patients eligible for treatment with Vargatef®. The objective of this NIS is to examine whether genetic/genomic markers (alone or combined with clinical covariates) could be used to predict OS in NSCLC patients eligible for treatment with Vargatef®. The investigations in this study are exploratory in nature and considered to be hypothesis generating. The results from these investigations may help to expand our understanding of the disease and the response to Vargatef®.

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8. RESEARCH QUESTION AND OBJECTIVES

The **primary objective** of the study is to generate hypotheses whether gene expression patterns (alone or combined with clinical covariates) or genetic markers could be used to predict OS in patients treated with Vargatef® according to the approved label.

Further objectives of the study are:

- to investigate potential association between the covariate "time since start of first line chemotherapy until start of Vargatef® therapy" and gene-expression patterns.
- to identify potential biomarkers, tumour genomic alterations and/or gene expression patterns to characterize the survival outcome potential of patients with late progression (≥ 9 months) versus early progression(< 9 months) from start of first line chemotherapy until start of Vargatef® therapy.

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9. RESEARCH METHODS

The intention of this NIS is to collect biomarker data in adult patients with NSCLC of adenocarcinoma histology, who failed first line chemotherapy and will be treated for their disease with Vargatef®, 200 mg twice daily (except the day of docetaxel infusion) in combination with docetaxel at 75 mg/m² every 21 days as indicated in the approved labels of Vargatef® and docetaxel.

9.1 STUDY DESIGN

This is a non-interventional, multi-country, multi-center, study based on newly collected data, in patients initiating Vargatef® for the first time (new users design) and followed up until death, lost to follow-up, withdrawal of consent or until required number of OS events has been reached, whichever occurs first.

In order to reflect real world usage of Vargatef® and outcomes, the choice of a non-interventional design is more appropriate than the experimental design. Moreover new data collection is also more appropriate to ensure adequate collection of gene expression patterns or genetic markers in combination with clinical characteristics, which may not be available or with insufficient accuracy in patient's medical records.

Per design, all included patients will be exposed to Vargatef® and docetaxel (according to Summary of Product Characteristics (SPC)).
As for any NIS, the assignment of the patient to Vargatef® or any other treatment falls within current practice and prior to the decision to talk to the patient about the study, so that the decision to prescribe Vargatef® is clearly separated from the decision to include the patient in the study. The decision of treatment, including the intended duration of treatment, is at the discretion of the physician providing care for the patient. Consequently, the medicines under observation are not provided by the marketing authorization holder.

Patients who qualify will be treated according to the approved label of Vargatef®: Vargatef® (200 mg administered twice daily except on the day of docetaxel infusion) in combination with docetaxel 75 mg/m² every 3 weeks for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy.

The primary outcome will be OS and a sample size of at least 300 evaluable patients is considered sufficient to fulfill the objective of this hypothesis-generating exploratory study. In order to account for possible non-evaluable patients up to 375 can be enrolled.

The analysis of OS will be conducted when 250 patients have had died. This is expected to occur after approximately 49 months from first patient in, assuming an accrual rate of 20 patients/month.

The end of the study will occur when the last patient has completed his/her follow-up visit and/or the required number of OS events has occurred, whichever occurs first. No further data will be collected afterwards (see Section 9.7.1).

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9.2 SETTING

The NIS will be conducted in about 100 oncology/pulmonology sites mainly in Europe which are experienced in lung cancer treatment. An average of 0.2 patient/month/site is expected. If patient recruitment takes longer than expected, the number of participating sites and the number of included patients per site may be increased.

Patient participation in this NIS is voluntary and it is not a prerequisite to be treated (see Section 9.1). Patients are treated according to the standard of care independent of their consent to participate in this NIS.

For tissue-derived investigations, samples of tumour tissue, obtained at diagnosis and/or at re-biopsy before the first line treatment initiation (either tumour blocks or slides, minimum of 10 slides and up to 20 slides if possible at 5µm thickness), will be collected after informed consent is given. Patient without tumour tissue are not eligible for participation in this NIS.

If tumour tissues are available from more than one time point, samples from the latest obtained biopsy before first line chemotherapy treatment should be provided whenever possible, assuming tumour quantity is equivalent.

If there are post-chemotherapy, re-biopsy samples at relapse, these should be provided, if available.

The site (primary tumour or metastatic site) and the date when the original tumour tissue was collected will be recorded in the electronic Case Report Form (eCRF).

During patient`s blood withdrawal, included in the regular clinical laboratory assessment, additional blood amount of 2 milliliters (ml) will be collected at baseline or at any time after Vargatef® initiation for blood derived investigations. No additional puncturing will be required and samples will only be used after signed informed consent. If blood sample is not available, a buccal swab may be requested.

Patient bio specimens will be sent for storage and analysis to BI or a central laboratory qualified and approved by BI.

Collected samples might be kept for up to 15 years according to local guidelines and regulations (see Section 9.3.3 for details). Storage location and identification of the samples will be adequately documented.

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9.2.1 Selection of study population

Inclusion criteria:

All consecutive patients can be included if all the following criteria are present:

- Age ≥ 18 years.
- Women and men with locally advanced, metastatic or locally recurrent NSCLC with histology of adenocarcinoma.
- Signed and dated written informed consent.
- Vargatef ® is initiated and administered in accordance with the SPC.
- Available fixed and paraffin embedded (FPE) tumour tissue routinely obtained at diagnosis and/or at re-biopsy before the initiation of the first line treatment (either block or slides, minimum of 10 slides and up to 20 slides if possible at 5µm thickness).

Exclusion criteria:

Patient won't be included if any of the following criteria is present:

- Any contraindication to Vargatef® or docetaxel as specified in their respective labels.
- Vargatef® initiated more than 7 days prior to inclusion in this NIS.
- Patients participating simultaneously in a clinical trial.

No additional medical procedures are required other than those which the patients would have received even if they were not included in the NIS. The treatment, as well as the diagnosis and monitoring procedures, follow the standard medical treatment practice.

There is therefore no risk to participating patients over and above the usual treatment risk with therapy with Vargatef® in combination with docetaxel.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the study site irrespective of whether they have participated in the NIS or not.

BI reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site.
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any administrative reason.
3. Violation of Good Clinical Practice (GCP) (as applicable), the Study Protocol, or the contract by a study site or physician, disturbing the appropriate conduct of the study.

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

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9.2.2 Details of study procedures

The study procedures will consist of:

- a baseline visit (if the patient is eligible for the study), visit from docetaxel administration up to 7 days after Vargatef® treatment initiation.
- and follow-up visits – every 6 months (± 1 month) until death or the end of the study, whichever occurs first.

9.3 VARIABLES

The following variables will be collected during the study according to different time points:

A. Baseline visit - The baseline visit is the visit from docetaxel administration up to 7 days after Vargatef® treatment initiation.

The following will be obtained and/or performed:

- Informed consent.
- Demographics (sex, birth date).
- Medical history (oncological, relevant non-oncological, smoking status, comorbidities, Epidermal Growth Factor Receptor (EGFR) mutation and Anaplastic Lymphoma Kinase (ALK) translocation status) and other mutations, if available.
- Eastern Cooperative Oncology Group performance score (ECOG).
- Start and end date of first line chemotherapy and drugs used.
- Date of progression in first line chemotherapy.
- Best response to first line chemotherapy (according to RECIST 1.1(R09-0262) if possible).
- Start and end date of other prior anti-cancer treatment (excluding chemotherapy) and drugs used.
- Date of progression under prior other anti-cancer treatment.
- Best response to prior other anti-cancer treatment (according to RECIST 1.1(R09-0262) if possible).
- Start date of docetaxel and Vargatef® treatment.
- Lactade Dehydrogenase (LDH) level measured within the last 7 days, if available.
- Percentage of Programmed death-ligand 1 (PD-L1) positive tumour cells, percentage of PD-L1 positive immune cells and type of diagnostic anti PD-L1 antibodies, if available.
- Ensure that tumour sample (paraffin block or tissue slides) is available for collection at any time during the study, including data on the site (primary tumour or metastatic site) and the date when the original tumour tissue was collected.
- During patient`s blood withdrawal, included in the regular clinical laboratory assessment, additional blood amount of 2 ml will be collected at baseline or at any time after Vargatef® initiation for blood derived investigations. No additional puncturing will be required and samples will only be used after signed informed consent. If blood sample is not available, a buccal swab may be requested.

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B. Follow-up visits – every 6 months (± 1 month) until death or the end of the study whichever occurs first.

- If the blood sample is not collected at the baseline visit, during patient's blood withdrawal, included in the regular clinical laboratory assessment, additional blood amount of 2 ml will be collected at any time after Vargatef® initiation for blood derived investigations. No additional puncturing will be required and samples will only be used after signed informed consent. If blood sample is not available, a buccal swab may be requested.
- Date of progressive disease (according to RECIST 1.1(R09-262) if possible).
- Subsequent anti-cancer therapy (start/stop date and dosage) after stop of Vargatef® and docetaxel.
- Dates and reason of Vargatef® and/or docetaxel discontinuation.
- Best response after Vargatef® and docetaxel treatment (according to RECIST 1.1(R09-262) if possible).
- Date of death.
- All Adverse Drug Reactions (ADRs) (serious and non-serious).
- All AEs with fatal outcome.

9.3.1 Exposure

Patients will be exposed to Vargatef®, 200 mg twice daily, except the day of docetaxel infusion in combination with docetaxel at 75 mg/m² every 21 days as indicated in the approved labels of Vargatef® and docetaxel.

9.3.2 Effectiveness outcome

1. Overall Survival (primary outcome)

OS is defined as the time from start of entering the study to time of death (irrespective of reason). The OS will be defined as follows:

- For patients with known date of death (regardless of the cause of death):
  OS [days] = date of death – date of treatment start + 1.
- For patients known to be alive by the end of study or follow-up visit:
  OS (censored) [days] = date of last contact when the patient is known to be alive – date of treatment start + 1.

2. Time since start of first line therapy until start of Vargatef® therapy

Time since start of first line therapy until start of Vargatef® therapy is divided into 2 subgroups as follows:

- "Late progression group": time from start of first line therapy until start of Vargatef® ≥9 months (T≥9)
- "Early progression group": time from start of first line therapy until start of Vargatef® <9 months (T<9)

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9.3.3 Covariates (biomarkers)

In this NIS explorative biomarkers will be investigated. These analyses are hypothesis generating and will be used to expand our understanding of the disease and study drug.

Expression profiling and genomic characterization of tumour tissue
FPE tumour tissue (either block or slides, minimum of 10 slides and up to 20 slides if possible at 5µm thickness), obtained at diagnosis and/or at re-biopsy before the first line treatment initiation will be required for global analysis of gene expression (e.g. but not limited to angiogenesis-related pathway genes, drug target genes and NSCLC driver genes). In addition, tumour samples will be analysed if tissue quantity and quality permits for mutations in a panel of cancer and Vargatef® target genes, e.g. VEGFR 1-3, FGFR1-3, PDGFRα&β, Ret, Kit, BRAF, NRAS, HER2, KRAS, EGFR, ALK, PIK3CA, ROS and for expression of e.g. PD-L1 and CD133. Moreover, if tumour tissue quantity and quality is sufficient additional markers related to the disease or drug response and resistance mechanisms will be assessed.

Genomic evaluation of blood samples
One blood sample should be collected at baseline or at any time after Vargatef® treatment initiation as a part of the regular/routine clinical laboratory assessment if possible for genomic analyses. The blood sample (approximately 2 ml in an EDTA tube) is a reference (normal tissue) to distinguish tumour-acquired somatic mutations and will be analyzed for the same set of genes as the tumour tissue (see above). In addition, variants in angiogenesis-related and/or drug target genes (e.g. VEGF-A, VEGFR1) will be analyzed if sample amount and quality permits. If blood sample is not available, a buccal swab may be requested.

Analytical determinations from tumour tissue and blood samples
From tumour tissue and blood or buccal swab samples nucleic acids (Deoxyribonucleic acid and Ribonucleic acid) will be extracted and analyzed according to standard molecular genetic methods and technologies. Assessment of protein markers e.g. PD-L1 and CD133 if tumour tissue quantity and quality is sufficient will be performed according to qualified histological methods and technologies.

In case patients do not consent to optional biobanking (see below) all remaining material, including blood, tissue, isolated deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) from these blood and tumour samples will be destroyed no later than three months after final report archived (i.e. study end).

Detailed instructions for sampling, handling and shipment of samples will be provided in the lab manual.

The biomarker analyses will be performed by BI or a qualified and BI approved central laboratory.

Biobanking (optional)
If quantity of blood samples and tumour tissue allows after initial prespecified analysis (see above) and separate optional consent is agreed upon by the patient, remaining material (e.g. isolated RNA and DNA) will be stored at BI or a qualified and approved CRO for up to

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fifteen (15) years after the end of the study according to local guidelines and regulations. Storage location and identification of the samples will be adequately documented. These samples will be used for future research to evaluate additional biomarkers that may elucidate further understanding of the disease or the study drug.

9.3.4 Safety

Safety will be collected with a focus on the following variables:

- all (ADR) (serious and non-serious),
- all AEs with fatal outcome.

How to collect and report AEs including the definitions are described in Section 11.

9.3.5 Other

Baseline characteristics
The following variables based on physician's report will be considered as important baseline characteristics and potential risk factors for the events of interest.

Demographics:

- Age
- Sex
- ECOG
- Smoking history
- Oncological history
- Date of first diagnosis
- Start and end date of first line chemotherapy and the drugs used
- Date of progression in first line chemotherapy
- Best response to first line chemotherapy
- Start and end date of other prior anti-cancer treatment (excluding chemotherapy) and the drugs used
- Date of progression under other prior anti-cancer treatment
- Best response to prior other anti-cancer treatment
- Start date of docetaxel and Vargatef® treatment
- Disease stage (locally advanced versus metastatic) at start of Vargatef® treatment
- Presence of adrenal metastasis / liver metastasis
- Number of metastatic organs
- LDH level measured within the last 7 days, if available.
- Percentage of PD-L1 positive tumour cells, percentage of PD-L1 positive myeloid cells and type of diagnostic anti PD-L1 antibodies, if available.

9.4 DATA SOURCES

NIS with new data collection.

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9.5 STUDY SIZE

Assuming that there is only one dichotomized genetic/genomic marker that divides the population into a biomarker positive (b+) or biomarker negative (b-) subgroup, the study is sized as such that the probability of detecting a true survival difference between these two biomarker groups is sufficiently large, while the probability of erroneously observing a survival difference is small.
Table 9.5: 1 summarizes the associated probabilities for observing HRs (i.e., the survival differences between the subgroups defined by the biomarker) below prespecified thresholds based on the assumption that a true survival difference is characterized by a HR of 0.85 and that no survival difference is characterized by a HR of 1 between the two groups for different numbers of OS events. We further assume that the distribution of biomarker subgroup b+ versus b- is 70% and 30%, respectively.

Table 9.5: 1 Probabilities for observing HRs for survival differences between the biomarker subgroups below prespecified thresholds

	True HR* 0.85			**True HR* 1.00**		
	Probability of observing a HR below prespecified threshold			Probability of observing a HR below prespecified threshold		
OS events	**0.9$**	**0.95$**	**1.0$**	**0.85$**	**0.9$**	**0.95$**
200	0.64	0.76	0.85	0.15	0.25	0.37
250	0.66	0.79	0.88	0.12	0.22	0.36
300	0.68	0.81	0.90	0.10	0.20	0.34

*HR for biomarker positive versus biomarker negative group $prespecified thresholds.

The calculations are based on the approximate normal distribution of the estimated log HR. With 250 OS events, if the true survival differences between the biomarker subgroups is characterized by a HR of 0.85, the probability of observing a HR≤0.9 is 66% and the probability of observing a HR ≤0.95 is 79%, while the risk of erroneously observing a HR>1 is only 12%. However, if there is no survival difference between the two biomarker subgroups, the risk of erroneously observing a HR≤0.85 or ≤0.9 is only 12% and 22%, respectively.
Assuming a recruitment rate of 20 patients per month (15 months accrual duration), a 10% drop-out rate, and a median OS of 11 versus 13 months (HR=0.85) for the biomarker subgroups, the observation of 250 OS events in a study with 300 patients is estimated to occur after approximately 49 months (see Clinical Trial Report (CTR) 1199.13,U13-1504-01)
These sample size calculations are based on the assumption of only one dichotomized genetic/genomic marker. Indeed, several genetic/genomic markers will be evaluated in this study, thus multiplicity issues will need to be considered.
Still, the sample size of at least 300 evaluable patients is in line with biomarker studies from literature. In the paper published by the Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma (R14-1926), gene expression-based survival prediction was investigated based on 442 lung adenocarcinoma patients with particularly investigating subgroups of patients according to the staging of their disease. Even this large

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study was not powered to make inferences with statistical confidence, but nevertheless provided interesting trends. Therefore, without accounting for a subgroup as staging of their disease in our study, a sample size of at least 300 evaluable patients is considered sufficient to fulfill the objective of this hypotheses-generating exploratory study. In order to account for possible non-evaluable patients up to 375 can be enrolled.

9.6 DATA MANAGEMENT

Patients' data will be gathered by Remote Data Capture (RDC) system.
The data management procedures to ensure the quality of the data are described in detail in the Statistical and Epidemiological Analysis Plan (SEAP) available in TMF.

9.7 DATA ANALYSIS

The primary objective of the statistical epidemiological analysis is to generate hypotheses whether gene expression patterns (alone or combined with clinical covariates) or genetic markers could be used to predict OS.

Further objectives of the study are:

- to investigate potential associations between the covariate "time since start of first line therapy until start of Vargatef® therapy" and gene-expression patterns;
- to identify potential biomarkers, tumour genomic alterations of gene and/or gene expression patterns to characterize the survival outcome of patients with late progression (≥ 9months) versus early progression (<9months) from start of first line therapy until start of Vargatef® therapy.

Predefined Subgroups:
Time since start of first line therapy until start of Vargatef® therapy is divided into 2 subgroups as follows:

- "Late progression group": time from start of first line therapy until start of Vargatef® therapy ≥9 months (T≥9)
- "Early progression group": time from start of first line therapy until start of Vargatef® therapy <9 months (T<9)

Additional subgroups based on the available biomarker variables and clinical covariates will be defined if deemed necessary.

Analyses on predefined or additional subgroups will be only performed if the number of subjects per group is sufficient.

All subjects entered with evaluable biomarker data value will be included in the statistical analyses.

Descriptive Statistics
The following descriptive statistics will be calculated for all continuous biomarkers, for all subjects and by subgroup (T≥9 vs T<9) at available time points : N, arithmetic mean, standard deviation, minimum, median, maximum, percentiles, arithmetic coefficient of variation.
For all categorical biomarkers frequency tables will be calculated.

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Furthermore, correlations among biomarkers and/or clinical covariates will be evaluated.

9.7.1 Analysis of efficacy

The median and range of OS and other descriptive statistics will be calculated (Kaplan-Meier estimates).

Table 9.7.1: 1 describes how patients will be classified for the analysis of death. Patients will be censored at the date of last contact if the physician is no longer able to contact a patient or caregiver, and vital status cannot otherwise be determined.

Table 9.7.1: 1 Outcome determination for OS

Situation	Outcome (event or censored)	Date of death or censoring
Patients died and the date of death is known	event	Date of death
Patients died and date of death is unknown	censored	Date of last contact when the patient is known to be alive
Patient alive	censored	Date of last contact
Unknown	censored	Date of last contact when the patient is known to be alive

Patients who are enrolled, but never received the combination therapy of docetaxel and Vargatef® therapy will be censored on the day of enrollment.

Additional clinical factors that might be relevant and included as covariates and/or used as subgroups in the models below will be pre-specified in the SEAP.

9.7.2 Statistical models for analyzing associations of biomarker with OS

Biomarkers will be investigated by univariate and multivariate prediction models and regression analysis.
For all univariate screening approaches, multiplicity correction of p-values will be performed.

Model performances will be quantified and uncertainty will be evaluated by resampling methods.

Categorical biomarkers will only be investigated provided there are sufficient patient numbers within the subgroups defined by the categorical biomarkers. For all selected categorical biomarkers the estimate of the HR/odds ratio and its 95% confidence interval (CI) will be presented. For continuous biomarkers the HR/odds ratio for a change per unit will be presented.

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9.7.2.1 Univariate screening approaches

Model to identify potential prognostic markers

The association between a biomarker and the efficacy endpoint OS will be explored by Cox's proportional hazard model.

For all biomarkers the hazard function h_i of the i^{th} patient is modeled as

$$h_i(t) = h_0(t) \cdot \exp(\beta_B \cdot B_i) \qquad \text{(Model 1)}$$

where

t Time point
h_0 Baseline hazard function
β_B Effect of biomarker

Other known prognostic factors, e.g. "time since start of first line until start of Vargatef® therapy", might be added to the model above, if applicable.

The Cox proportional-hazards models will be used to derive the estimates and 95 % CIs for the HR.

Logistic Regression Model

The logistic regression model will be used to characterize the pre-defined subgroup by biomarkers measured at diagnosis. The probability of being in the subgroup T< 9 will be investigated for each biomarker separately.
For all biomarkers measured at diagnosis the probability of being in one or the other subgroup will be calculated using a logistic regression model, with
$Pr(Y_i = y_i \mid B_i) =$

p_i, if $y_i = 1$, i.e. the i-th patient is in the subgroup (T<9)
$1 - p_i$, if $y_i = 0$, i.e. the i-th patient is in the subgroup (T>=9)

$$\text{logit}(p_i) = \ln(p_i / (1-p_i)) = ß_0 + ß_1 B_i \qquad \text{(Model 2)}$$

where

$ß_0$ Intercept
$ß_1$ Effect of Biomarker

The Logistic regression models will be used to derive the estimates and 95 % CIs for the odds ratio.

9.7.2.2 Multivariate approaches

To identify prognostic biomarker signatures based on gene-expression and genomic alterations, multivariate Cox regression modelling and/or other regression models in combination with variable selection or alternative multivariate approaches will be used.

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9.7.3 Analyses of biomarkers

Investigation of gene-expressions and gene-expression-signatures to predict OS

Gene-expressions will be investigated as prognostic biomarkers (see Section 9.7.2) in different scenarios:
Univariate approaches:

- gene-expression can predict OS in all patients (Model 1)
- gene-expression and basic clinical covariates can predict OS in all patients (Model 1)
- gene-expression can characterize predefined subgroups (T≥9 vs T<9) (Model 2)

Multivariate approaches:

- gene-expression-signatures can predict OS in all patients (see Section 9.7.2.2)
- gene-expression-signatures and basic clinical covariates can predict OS in all patients (see Section 9.7.2.2)

Correlations between "time since start of first line until start of Vargatef® therapy" and gene-expression patterns will be assessed using correlation coefficients.

Investigation of tumour genomic alterations to predict OS (if quality and amount of data permits)

To investigate the potential of tumour genomic alterations as prognostic biomarkers, each selected biomarker (dependent on the frequency threshold of appearance, i.e. mutation must be present in a reasonable amount of patients) will be analysed separately (see Section 9.7.2.1).

To investigate the potential of tumour genomic alterations as prognostic biomarker signatures, selected biomarkers (dependent on the frequency threshold of appearance, i.e. mutation must be present in a reasonable amount of patients) will be analysed (see Section 9.7.2.2).

Additional exploratory analysis for biomarkers will be specified in the SEAP.

9.7.4 Analyses of safety

The safety analysis will include all patients registered in the study and receiving the Vargatef® treatment. In general, safety analyses will be descriptive in nature, will be based on BI standards, and will focus on ADRs related to the Vargatef® treatment.
AEs will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA). All AEs occurring between first intake of Vargatef® prescribed at baseline visit and till the patient leaves the study will be collected (see Section 9.10.4). An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses that there is a reasonable possibility for causal relationship to Vargatef®.

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The frequency of AEs/ADRs will be tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics, if deemed necessary (see Section 9.3.4).
No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.

9.7.5 Handling of missing data

Missing biomarker data will not be imputed. Missing data for OS will be handled according to Table 9.7.1: 1.

9.8 QUALITY CONTROL

All entries in the eCRF and the existing codings will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the study site.
Plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk/doctor.
If corrections are necessary after the data are saved, these will be documented in an audit trail.
For the further quality assurance of the documented patient observations, a sample-based source data comparison will be performed on about 30% of included patients. An additional inspection/quality assurance check of this NIS can be performed in case of any deviation.

9.9 LIMITATIONS OF THE RESEARCH METHODS

As for any NIS, the study may be subject to biases. The main anticipated one is related to selection bias. Indeed, the study objectives may bias the selection of patients especially because of the required minimum number (10) of tumour tissue slides to be included. This minimum number is a trade-off between what would be considered as the lowest possible number of slides to ensure the goals of the study will be reached and the number of patients that may not be included into the study just because of insufficient number of archived slides. However, consultations with experts in the field have shown that this figure is often what is collected in routine practice. So the impact should be limited in the selection of patients. As the extent of this potential selection bias in a NIS with new data collection may be difficult to quantify, methodological efforts have been taken to reduce it. As an example, physician will be asked to include all consecutive patients that fit with inclusion criteria. As a consequence, a small amount of information will be collected for all patients considered for the study on a screening log and entered in the study database in order to describe the extent of such potential selection bias. This information will be very minimal and non-identifiable since it will be collected outside the patient's consent; so limited to patient's age range, gender and reason for non-inclusion (consent not provided, not enough archived tumour tissue slides or other reason). Comparing this information with the one of included patients will allow us to quantify any potential selection bias.

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9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRB) / Independent Ethics Committee (IEC) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the physician's study-related files and correspondence, and the informed consent documentation of this NIS.

9.10.2 Records

eCRFs for individual patients will be provided by the sponsor (BI), via remote data capture.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the physician's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.
Transfer of the results from the biomarker and pharmacogenomics analysis to the clinical data warehouse will be done by Clinical Data Repository (CDR).

9.10.2.2 Direct access to source data and documents

The physician / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. Food and Drug Administration (FDA)). The CRA / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.3 Statement of confidentiality

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

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 study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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9.10.4 Patient completion

The collection of the data per patients will continue until death or lost to follow-up, withdrawal of consent or until the required number of OS events has been reached.
At the earliest of the above criteria, the Patient Completion information should be completed in the eCRF.

9.10.5 Completion of study

The end of the study will occur when the last patient has completed his/her follow-up visit and/or the required number of OS events has occurred, whichever occurs first (see Section 9.7.1). No further data will be collected afterwards.

The EC/ Competent Authority (CA) in each participating EU member state needs to be notified about the end of the study (last patient/patient out) or early termination of the study.

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10. PROTECTION OF HUMAN SUBJECTS

10.1 INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for GCP (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The physician should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the physician and of the sponsor with regard to publication of the results of this study are described in the physician contract. As a general rule, no study results should be published prior to finalization of the Study Report.

10.1.1 Study approval, patient information and informed consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective IRBs/IECs and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent retained by the physician as part of the study 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.

The patient must be informed that his/her personal study-related data will be used by BI in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CTM/CRA) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An 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 a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. 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.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AE of Special Interest (AESI)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this

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study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The physician shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional studies are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

- all ADRs (serious and non-serious)
- all AEs with fatal outcome

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The physician carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of AE
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment 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 **a reasonable 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 etiologies that could explain the event (e.g. preexisting 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).

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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; 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 study drug treatment continues or remains unchanged.

Intensity of AE
The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy
In rare cases, pregnancy might occur in a study. Once a female subject has been enrolled into the study, after having taken study medication, Vargatef® , the physician must report any drug exposure during pregnancy to the sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the physician on the NIS AE form from signing the informed consent onwards until the end of the study:

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Table 11.2: 1 Report types and timelines

Type of Report	Timeline
All **Serious Adverse Drug Reactions** (SADRs) associated with the nintedanib	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to nintedanib	immediately within 24 hours
All **non-serious ADRs** associated with the nintedanib	7 calendar days
All pregnancy monitoring forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the physician could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required
For each reportable AE, the physician should provide the information requested on the appropriate (e) CRF pages and the NIS AE form.

Reporting of related AEs associated with any other BI drug
The physician is encouraged to report all AEs related to any BI drug other than the Vargatef® according to the local regulatory requirements for spontaneous AE reporting at the physician's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 TIME WINDOWS

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

11.4 DOCUMENTATION OF ADVERSE EVENTS AND PATIENT NARRATIVES

Expedited reporting of Serious Adverse Events (SAE), e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IRBs/IECs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

BI intends to use data from this study to prepare peer-reviewed publications and other scientific communications such as abstracts, posters, and podiums presentations.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A non-interventional biomarker study in patients with Non-Small Cell Lung Cancers (NSCLCs) of adenocarcinoma tumour histology eligible for treatment with Vargatef® according to the approved label.

Study reference number:
1199.223

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	11
1.1.2 End of data collection[2]	☒	☐	☐	11
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	11
1.1.6 Final report of study results.	☒	☐	☐	11

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

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Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	12,13
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16,17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	13,19

Comments:
The primary objective of the statistical epidemiological analysis is to generate hypotheses.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15,16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	11,15
4.2.2 Age and sex?	☒	☐	☐	17
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	15,16
4.2.5 Co-morbidity?	☒	☐	☐	17,18
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	17

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	19

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Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	18,19,20
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	18,19,21
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	18,19,21
8.1.3 Covariates?	☒	☐	☐	18,19,21
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	18,19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	18,19
8.2.3 Covariates? (e.g. age, sex, clinical and drug use				

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Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	18,19
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21,22

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	24,25
10.3 Are descriptive analyses included?	☒	☐	☐	23
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	24,25
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27
11.3 Are methods of quality assurance described?	☒	☐	☐	27
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

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Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	26,27
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	16
12.3 Does the protocol address other limitations?	☐	☒	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	29
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	29

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

Name of the main author of the protocol: _____

Date: 15/9/2015

Signature:

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ANNEX 3. ADDITIONAL INFORMATION

ANNEX 3.1 ECOG PERFORMANCE STATUS

Grade	Definition
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,
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up to about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead

APPROVAL / SIGNATURE PAGE

Document Number: c03352377 **Technical Version Number:2.0**

Document Name: 1199-223--protocol

Title: A non-interventional biomarker study in patients with Non-Small Cell Lung Cancer (NSCLC) of adenocarcinoma tumour histology eligible for treatment with Vargatef according to the approved label

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader		10 May 2019 09:38 CEST
Approval- Safety Evaluation Therapeutic Area		10 May 2019 10:37 CEST
Author-Trial Statistician		10 May 2019 11:08 CEST
Approval-Translational Medicine Expert		10 May 2019 11:23 CEST
Approval-Team Member Medicine		10 May 2019 13:16 CEST
Approval-Therapeutic Area		10 May 2019 17:09 CEST
Approval- of Global Epidemiology		13 May 2019 16:55 CEST
Verification-Paper Signature Completion		15 May 2019 08:29 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed