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Clinical Study Synopsis for Public Disclosure

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1. 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			
Report date: 07 July 2020	**Study number:** 1199.223	**Version/Revision:** 01	**Version/Revision date:** Not applicable
Title of study:	LUME-BioNIS: A non-interventional biomarker study in patients with NSCLC of adenocarcinoma tumour histology eligible for treatment with Vargatef® according to the approved label.		
Keywords:	Biomarkers Non-small-cell lung cancer (NSCLC)-adenocarcinoma Nintedanib/docetaxel		
Rationale and background:	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) was to explore predictive genetic or genomic markers (alone or combined with clinical covariates) in patients with NSCLC who were eligible for treatment with Vargatef®. All analyses were exploratory in nature and hypothesis-generating.		
Research question and objectives:	To explore whether genetic or genomic markers (alone or combined with clinical covariates) could be used to predict overall survival in patients with NSCLC treated with Vargatef® according to the approved label.		
Study design:	Non-interventional, multi-national, multi-site study based on newly collected data in patients who, for the first time, received Vargatef® as part of the routine treatment according to the approved label (new users design). Patients were planned to be followed until they died, were lost to follow-up, withdrew consent, or until the required number of overall survival events had occurred, whichever occurred first. As agreed with the EMA, the study was terminated earlier.		
Setting:	The study period was from 14 Mar 2016 (first patient in) to 03 Sep 2019 (last patient out). Patients were treated 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.		

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Subjects and study size, including dropouts:	Adults with locally advanced, metastatic or locally recurrent NSCLC with histology of adenocarcinoma could be included. Eligible for the study were patients who were assigned to Vargatef® treatment as part of their routine treatment according to the approved label. Patients had to have 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. The study was conducted at 71 sites in 13 countries: Austria, Belgium, Denmark, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, Netherlands, Spain, Sweden, and UK. The participating hospitals had oncologists/pulmonologists available. Enrolment period was from 14 Mar 2016 to 19 Oct 2018. Altogether 295 patients were screened, 260 patients were entered into the study, and 257 patients were treated with Vargatef® and docetaxel.		
Variables and data sources:	Primary outcome: Overall survival in relation to exploratory biomarker assessment, including gene-expression and genomic alterations. NIS based on new data collection (NISnd). This is the primary analysis after the end of the study. There was no interim analysis. *Statistical methods* Multivariate biomarker variable selection was based on overall survival (OS) only. IPF LASSO (main biomarker analysis) was applied with 2 modalities, in addition standard LASSO was performed for multivariate analyses. Univariate analyses were performed for gene expression-based pathways and cell types plus selected individual angiogenesis genes (but not for each single gene), DNA alterations by gene, putative tumour mutational burden, immunohistochemistry, genotyping, and the clinical covariates for OS and progression-free survival (PFS). 'Time since the start of first-line chemotherapy until the start of Vargatef® therapy' (further objective) and 'PD as best response to first-line therapy' were analysed with the same multi- and univariate methods as the biomarkers for OS. All biomarker analyses were performed on the biomarker evaluation set (BES).		

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Results:	*Disposition* Altogether 257 patients received at least 1 dose of Vargatef® and docetaxel. At the end of the study, all patients had permanently discontinued Vargatef® and docetaxel. Reasons for discontinuation of Vargatef® were progressive disease (60.7%), adverse events (26.5%), lost to follow-up (0.4%), and other (12.5%). Reasons for discontinuation of docetaxel were progressive disease (35.8%), adverse events (17.9%), and other (46.3%). *Demographics* The median age (range) of the patients was 64.0 (31-83) years. Altogether 167 men (64.2%) and 93 women (35.8%) were included in the study. Almost all patients were White (White 98.5%; Asian 0.4%; missing 1.2%); most patients were not Hispanic/Latino (not Hispanic/Latino 80.0%; Hispanic/Latino 20.0%). Most patients were either ex-smokers (65.4%) or current smokers (26.5%). As required by the inclusion criteria, all patients (100.0%) must have had adenocarcinoma histology to enter the study. At diagnosis, the majority of patients (68.8%) had tumour stage IV (UICC/AJCC). Most patients (90.8%) had metastatic disease at baseline. Metastases were most often located in lymph nodes (52.7%), lung (ipsilateral 37.3%; contralateral 30.8%), bones (37.3%), and liver (23.1%). ECOG performance score was 0 (31.2%) or 1 (54.6%) for most patients; it was 2 for 12 patients (4.6%). Prior immunotherapy was given to 67 patients (25.8%). *Exposure* Most patients (88.1%) were assigned to docetaxel at a dose of 75.00 mg/m² every 21 days. The median total treatment duration (range) with Vargatef® was 12.9 (0-111) weeks. The frequency of patients with at least 1 Vargatef® dose reduction was 16.9%. The median time to the first Vargatef® dose reduction (range) was 8.9 (1-46) weeks. *Compliance* Important protocol deviations were identified in 23.1% of patients: 48 patients (18.5%) did not meet the entrance criteria; 15 patients (5.8%) did not take Vargatef® according to the label.		

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Results (cont.):	*Efficacy results* In total, 79.2% of patients had an OS event. The median OS time (P25, P75) was 8.08 (3.94, 14.00) months. For the analysis of OS, 20.8% of patients were censored at the date of the last contact. The median follow-up time (95% CI) was 19.65 (17.84, 22.08) months. The 1-year survival rate (95% CI) was 34.2 (0, 89.4)%; the 2-year survival rate (95% CI) was 11.6 (6.3, 18.8)%. In total, 95.0% of patients had a PFS event. The median PFS time (P25, P75) was 3.71 (1.38, 6.24) months. For the analysis of PFS, 86.2% of patients had disease progression, 8.8% of patients had died, and 5.0% of patients were censored. The 3-months PFS rate (95% CI) was 55.6 (43.5, 66.2)%, the 6-months PFS rate (95% CI) was 27.6 (9.3, 49.8)%, the 9-months PFS rate (95% CI) was 14.2 (8.5, 21.3)%, and the 12-months PFS rate (95% CI) was 6.0 (3.6, 9.4)%. Disease control was observed for 58.7% of patients with a tumour response: 14.6% of patients showed an objective response (partial response), 44.1% of patients showed stable disease. A *post hoc*, exploratory analysis of the subgroup of patients with prior immunotherapy revealed evidence of efficacy: the median PFS was 4.62 months for the 67 patients with prior immunotherapy and 3.22 months for the 193 patients without prior immunotherapy. Similarly, the median OS for patients with prior immunotherapy was 8.84 months vs 7.79 months for patients without prior immunotherapy. The disease control rate was 78.2% for the group of patients with prior immunotherapy vs 51.9% for the group of patients without prior immunotherapy. *Biomarker results* The primary statistical analysis of the numerous clinical and molecular biomarkers was pre-specified as being the IPF-LASSO multivariate analysis. Analysis of OS in the IPF-LASSO multivariate analysis only revealed the following clinical co-variates as factors associated with the prediction of OS: 'brain metastases' (Metastatic sites of the brain: yes vs no or missing), 'liver metastases' (Metastatic sites of the liver: yes vs no or missing), and 'number of metastatic sites' (Number of metastatic sites at baseline: ≤2 or missing vs >2).		

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Results (cont.):

Safety results

Most patients (79.8%) were reported with at least 1 AE/ADR during the on-treatment period; an overall summary is provided in the table below.

	Vargatef®
Patients, N (%)	257 (100.0)
Any AE/ADR	205 (79.8)
Drug-related AEs/ADRs (investigator-assessed)	130 (50.6)
Other significant AEs/ADRs (ICH E3)	59 (23.0)
AEs/ADRs leading to dose reduction or discontinuation of Vargatef®	123 (47.9)
AEs/ADRs leading to Vargatef® dose reduction	22 (8.6)
AEs/ADRs leading to Vargatef® discontinuation	110 (42.8)
Serious AEs/ADRs [1]	127 (49.4)
Fatal	89 (34.6)
Immediately life-threatening	5 (1.9)
Resulted in disability or permanent damage	0
Required hospitalisation	61 (23.7)
Prolonged hospitalisation	8 (3.1)
Congenital anomaly	0
Other	2 (0.8)
Worst intensity of AEs/ADRs	
Mild	20 (7.8)
Moderate	63 (24.5)
Severe	122 (47.5)

All ADRs (serious and non-serious) as well as fatal AEs were collected.
[1] More than 1 seriousness criterion might be given for each patient.

The most frequent AEs/ADRs by system organ class (SOC) were gastrointestinal disorders (42.4%), neoplasms benign, malignant and unspecified (26.1%), and general disorders and administration site conditions (21.0%). The most frequent AEs/ADRs by preferred term (PT) were diarrhoea (29.6%), malignant neoplasm progression (25.7%), and nausea (10.5%).

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Results (cont.):	AEs/ADRs that led to Vargatef® dose reduction, reported in at least 2 patients, included the PTs diarrhoea (12 patients; 4.7%), nausea (4 patients; 1.6%), vomiting (2 patients; 0.8%), alanine aminotransferase increased (2 patients; 0.8%), aspartate aminotransferase increased (2 patients; 0.8%), gamma-glutamyltransferase increased (2 patients; 0.8%), transaminases increased (2 patients; 0.8%), and decreased appetite (2 patients; 0.8%). The most frequent AEs/ADRs that led to permanent treatment discontinuation by SOC were gastrointestinal disorders (14.8%); and neoplasms benign, malignant and unspecified (12.1%). The most frequent AEs/ADRs by PT were malignant neoplasm progression (11.7%) and diarrhoea (9.3%). The most frequent serious AEs/ADRs by SOC were neoplasms benign, malignant and unspecified (26.1%); and infections and infestations (9.7%). The most frequent serious AEs/ADRs by PT were malignant neoplasm progression (25.7%) and pneumonia (5.1%). Altogether 89 patients (34.6%) died during the on-treatment period of the study. The majority of the fatal events related to tumour progression and malignant neoplasm progression. The most frequent fatal AEs/ADRs by SOC were neoplasms benign, malignant and unspecified (24.9%); and infections and infestations (4.3%). The most frequent fatal AEs/ADRs by PT were malignant neoplasm progression (24.9%) and pneumonia (2.3%). The investigator considered all but 1 death to be not drug-related.		
Discussion:	In the non-interventional LUME-BioNIS study, Vargatef® plus docetaxel demonstrated real-world clinical effectiveness in patients with adenocarcinoma NSCLC previously treated with chemotherapy as well as both immunotherapy and chemotherapy. The *post hoc*, exploratory analysis of the subgroup of patients with prior immunotherapy suggests that the Vargatef® plus docetaxel combination treatment yields greater efficacy when administered after immune-checkpoint inhibitors than administered without prior immunotherapy.		

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Discussion (cont.):	Safety findings were as expected and consistent with the known safety profile of Vargatef® plus docetaxel in patients with advanced NSCLC. Despite comprehensive biomarker analyses (both clinical and molecular) using various analytic approaches, no new prognostic marker was identified for the OS outcome. Hence, no possible new predictive marker for OS was identified as well. Given the efficacy and safety results of this non-interventional study, the benefit-risk balance of Vargatef® plus docetaxel remains unchanged in the approved indication.		
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