CSR Synopsis

Protocol code	AIO-YMO/TRK-0415
Title	**Fostering efficacy of anti – PD-1 – treatment: Nivolumab plus radiotherapy in advanced NSCLC (FORCE)**
EudraCT No.	2015-005741-31
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Coordinating Investigator (LKP)	Dr. med. Farastuk Bozorgmehr Department of Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital Röntgenstrasse 1 69126 Heidelberg, Germany
First patient enrolled **Last patient enrolled** **Last patient completed**	21-MAR-2017 18-DEC-2019 30-DEC-2020
Regulatory Authority Vorlage-Nr.	Paul-Ehrlich-Institut 2828/01
Ethics Committee No.	Ethikkommission der Medizinischen Fakultät der Universität Heidelberg AFmu-399/2016
Study design	Open label, phase II trial
Objectives	***Primary objective*** To investigate efficacy of a nivolumab-radiotherapy combination treatment in metastatic non-squamous NSCLC patients. The objective response rate was defined as primary efficacy endpoint. ***Secondary objectives*** • to assess safety and tolerability of nivolumab in combination with radiotherapy • to collect further efficacy data in patients without necessity of radiotherapy • to collect further information on individual, patient reported and investigator-assessed quality of life • to explore immune related RECIST criteria as an evaluation method for clinical benefit of nivolumab and nivolumab/radiotherapy (PFS and ORR using assessment according irRECIST) ***Exploratory objectives*** *(will be presented in a separate report)* • To explore predictive biomarkers for the response to nivolumab in the tumor and serum including: o PD-L1 assessment o Phenotypical analysis of lymphocytes o Functional analysis of T-cells o Analysis of T-cell receptor specificities o Biomarker assessment of tumor IHC beyond PD-L1 o Soluble pro- and anti-inflammatory markers o Genomic profiling and gene expression profiling

	• To address the role of radiotherapy in the context of immune modulation, several aspects of radiation planning and treatment are planned to be explored. This includes both the location and composition of radiation targets and the anatomical profile of abscopally responding lesions. Therefore, treatment-related aspects characterizing the irradiated targets and abscopally responding target lesions will be documented by the treating radiation oncologist and radiologist.
Methodology	Adult patients with metastatic non-squamous NSCLC in 2nd -and 3rd -line treatment were included in this study. Patients with necessity of radiotherapy of a metastatic site (e.g., bone) were assigned to study group A, whereas patients without the necessity of radiotherapy were assigned to study group B. Patients in groups A and B received 240 mg fixed dose nivolumab q2w until disease progression (according to RECIST v1.1), unacceptable toxicity or patient withdrawal of consent. Patients in group A, in addition, received concurrent radiotherapy starting at the latest 72 h after the first nivolumab administration. Radiotherapy consisted of radiation dose of 4 Gy for a total of 5 courses during a two-week time interval (total dose of 20 Gy). Patients who demonstrated clinical benefit from nivolumab at time of end of active treatment, were allowed to continue on-label treatment at investigator's discretion in accordance with marketing authorization of nivolumab. Patients were assessed for adverse events by non-directive questioning at each visit. Adverse events also were detected when they were volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Adverse events were documented according to the CTCAE version 4.03. Additionally, relationship of an adverse event to the investigational agents was determined by the Investigator. SAEs were followed for up to 100 days post EOT. Radiographic tumor assessment (CT, MRI) was performed at baseline and then every 6 weeks beginning at week 9 for the first year and thereafter, every 12 weeks until documented disease progression. All patients were followed up for survival status and subsequent cancer therapies at least 12 months after EOT every 12 weeks. Quality of life assessments using FACT-L questionnaire were performed before any study procedures started and at every second cycle for the first 6 months, then every 6 weeks thereafter for another 6 months and then every 12 weeks until the end of treatment.
Number of patients (planned and analyzed):	Planned: Initial planned sample size: N=130 (65 per group). Analyzed: Due to changes of the standard of care therapy recruitment was stopped prematurely on 31-Dec-2019, with 101 patients enrolled. Group A – 41 Group B – 60
Key inclusion criteria	1. Age ≥ 18 years at time of study entry. 2. ECOG performance status 0-1. 3. Patients with metastatic non-squamous non-small cell lung cancer after failure of platinum-based doublet chemotherapy and a) no necessity of radiotherapy (group B) or b) the necessity of radiotherapy of a metastatic bone lesion or soft tissue lesion (group A) 4. Patients must have measurable disease by CT or MRI per RECIST 1.1 criteria. 5. For each patient a formalin fixed, paraffin-embedded tumor tissue block (archival or recent) or a minimum of 15 unstained slides of tumor sample (2-3 µm sections; slices must be recent and collected on slides

	provided by the sponsor) must be available for biomarker (PD-L1) evaluation. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.
Key exclusion criteria	1. Patients who require ongoing treatment with more than 10-mg of prednisone (or steroid equivalent, excluding inhaled or topical steroids) daily. 2. Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). 3. Patients with an active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger. (Subjects with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders, (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.) 4. Any serious or uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy (see protocol section 3.3 for details). 5. Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required or anticipated to be required during the study period. 6. Brain metastases mandating active treatment in terms of irradiation (whole brain irradiation or stereotactic brain irradiation). 7. Subjects with brain metastases are eligible if metastases have been treated and treatment has been completed at least 12 weeks before inclusion in this study for group B and 2 weeks for group A. Moreover, there must be no magnetic resonance imaging (MRI) evidence of progression within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. Patients with stable/asymptomatic brain metastases that do not require local therapy with irradiation (whole brain irradiation or stereotactic brain irradiation) can be included. In ambiguous cases, consultation with the LKP or his/her delegate is advised. 8. Known activating EGFR mutation or a known ALK translocation.
Test product, dose and mode of administration, batch number	<u>Nivolumab:</u> • Batch No.: AAK4481; AAN8159; AAG8273; AAU9327; AAX1033; AAZ0636; ABB6752 • Formulation: Nivolumab Injection, 100 mg/10 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentaacetic acid (pentetic acid), and polysorbate 80 (Tween 80), pH 6.0 and includes a 0.7-mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers, and sealed with aluminum seals. • Nivolumab study drug was given every two weeks at a dose of 240 mg to be administered as a 60-minute IV infusion. • Package size: 100 mg/10 mL (10 mg/mL) glass vials

	• Route of administration: intravenous infusion • Source: BMS
Duration of treatment:	Treatment with nivolumab alone or with concurrent radiotherapy was planned to be administered until disease progression (according to RECIST v1.1), unacceptable toxicity or patient withdrawal of consent.
Criteria for evaluation: Efficacy/ Safety	All patients enrolled, with study drug assignment designated according to initial assignment, regardless of whether patients receive study drug or receive a different drug from that to which they were assigned are considered the primary efficacy population and were analyzed accordingly. A patient receiving at least one dose of study medication was considered evaluable for safety.
Statistical methods:	This phase II trial was intended to investigate the efficacy of a nivolumab-radiotherapy combination in metastatic non-squamous NSCLC patients. The objective response rate (objective response defined as best overall response according to RECIST V1.1 criteria) was chosen as primary efficacy endpoint. The primary endpoint ORR was evaluated by reporting absolute and relative frequencies for both treatment groups. For group A, a binomial test was conducted at a one-sided significance level of α=0.05 in order to assess if the ORR exceeds 19%. Furthermore, one-sided 95%-confidence intervals were calculated for the ORR in both groups. For the secondary time-to-event outcomes overall survival and progression-free survival, median survival times and one-year rates were given with 95% confidence intervals and Kaplan-Meier curves were calculated for both treatment groups. For binary outcomes, relative and absolute frequencies were reported alongside the corresponding 95% confidence intervals for both groups, while for continuous outcomes the mean, standard deviation, median, interquartile range, minimum and maximum will be given alongside 95% confidence intervals for the mean. Descriptive sub-group analyses with regard to PD-L1 status were conducted assessing the primary and secondary outcomes separately for the patient strata PDL-1 high/low (e.g. cutoffs 1%, 5%, and 10%) by reporting the same statistical measures as described before for both treatment groups. Safety analysis included a tabulation of relative and absolute frequencies for adverse and serious adverse events.
SUMMARY CONCLUSIONS EFFICACY RESULTS:	Different analysis strategies (including imputed ITT and complete cases) revealed an ORR of 7-9% for patients with the necessity of radiotherapy of a metastatic site (group A) and an ORR of 23-27% for patients without this necessity (group B). Thus, the hypothesis that by combination of the treatment modalities an ORR of at least 19% can be achieved in both PD-L1-negative and –positive patients could not be confirmed. The significantly lower response rate to the nivolumab/radiation combination therapy is likely linked to the significantly poorer baseline clinical condition of patients in group A compared to group B, indicating a selection bias based on the clinical indication for local radiotherapy.
SAFETY RESULTS:	Despite the differences in the baseline characteristics, frequency and severity of treatment-related adverse events did not differ between both groups. Furthermore, no treatment-related SAEs with a fatal outcome were observed.
CONCLUSION:	The study design, which included patients with clinical indication for palliative radiotherapy, lead to a selection bias towards patients with unfavorable outcome characteristics. Combination of nivolumab and radiotherapy is safe and feasible; however, it does not improve ORR in patients with indication for radiation of metastases.
Date of the report:	30 March 2022