AIO-TRK-0219: Advancing Brigatinib Properties in anaplastic lymphoma kinase positive non-small cell lung cancer (ALK+ NSCLC) patients by deep phenotyping (APB)

AIO-Studie	
Studiennummer/-Code:	AIO-TRK-0219 - ABP-2019
Status:	In Rekrutierung
Rekrutierungszeitraum:	Seit Q1 2020, 36 Monate Rekrutierung
Zentren:	geplant: 20 initiiert: 26
Patienten:	geplant: 116 aktuell eingeschlossen: 69
Weitere Zentren:	Ggf. nach Rücksprache weitere Zentren möglich
Letzte Aktualisierung	März 2022

COORDINATING INVESTIGATOR (LKP)	Univ.-Prof. Dr. Michael Thomas, MD Dept. of Thoracic Oncology/Internal Medicine Thoraxklinik at Heidelberg University Röntgenstr. 1 D-69126 Heidelberg E-Mail: Michael.Thomas@med.uni-heidelberg.de
SPONSOR / PROJECT MANAGER	Institut für Klinische Krebsforschung IKF GmbH Steinbacher Hohl 2-26 60488 Frankfurt Dr. Regina Eickhoff E-Mail: eickhoff.regina@ikf-khnw.de
STUDY PHASE	Phase II trial
STUDY DESIGN	This is a prospective, randomized, open-label, multicenter phase II study.
PLANNED NUMBER OF PATIENTS	116, randomized 1:1 into both treatment arms (58 patients per arm)
STRATIFICATION FACTORS	• Presence of brain metastases vs no presence of brain metastases • ECOG 0-1 vs 2
TOTAL NUMBER OF STUDY SITES	Approx. 20 sites
STUDY POPULATION	Patients are eligible if they have newly-diagnosed histologically confirmed locally advanced (stage III) and not suitable for curative treatment, i.e. R0 operation or definitive chemoradiation, or metastatic (stage IV) ALK$^+$ NSCLC and an age ≥ 18 years.
STUDY AIM	To compare efficacy of brigatinib and other 2nd-generation ALK TKI in 1st and 2nd line and to explore resistance patterns according to treatment and molecular properties of the tumors.
PRIMARY OBJECTIVE AND ENDPOINT	Efficacy of 1st-line treatment, measured as: • Progression-free survival (PFS) of 1st-line treatment (RECIST v1.1)
SECONDARY OBJECTIVES AND ENDPOINTS	Efficacy of 1st and 2nd line treatment, measured as: • PFS of 2nd-line treatment (RECIST v1.1) • TNT 1st line (TNT1, i.e. time-to-next treatment for the 1st line, defined as the time from begin of 1st-line treatment until begin of 2nd-line treatment) • TNT 2nd line (TNT2, i.e. time-to-next treatment for the 2nd line, defined as time from begin of 2nd line until begin of 3rd-line

	treatment) • TNT1/2 (time-to-next treatmemt for the 1st and 2nd line together, defined as time from begin of 1st-line treatment until begin of 3rd-line treatment) • Overall survival (OS) • Efficacy in the central nervous system (CNS, "brain control") of 1st- and 2nd-line treatment assessed by applying RECIST v1.1 criteria o intracranial ORR (iORR) o intracranial DOR (iDOR) o time to intracranial progression (TTiP), defined as the time from start of 1st-line treatment until the occurrence of a new CNS lesion or progression of pre-existing CNS lesions (adjusted for the two competing events "death" and "extracranial progression inducing a change in ALK inhibitor treatment") Quality of life (QoL) as assessed by validated questionnaires: • QoL: SF-12 and EORTC-QLQ-BN20 (EORTC-QLQ-BN20 in case of brain metastases, only) Safety and tolerability
EXPLORATORY OBJECTIVES	• Typing of *ALK* fusion variants, assessment of *TP53* mutation status and detection of „acquired resistance" mutations via standardized next-generation sequencing (NGS)-based multiplex analysis • Efficacy of treatment according to *ALK* fusion variant and *TP53* status • Molecular resistance patterns after 1st-line failure • Impact of 2nd-line treatment after failure of 1st line • Clinical utility of cerebrospinal fluid ctDNA analysis in "brain-only" progression
TRANSLATIONAL RESEARCH	This clinical trial will be accompanied by a comprehensive translational research program. Tissue and blood sampling for molecular biomarker analyses: • Biopsies are collected at baseline (prior to start of 1st-line treatment); in addition, biopsies of lesions appearing or enlarging under treatment are strongly recommended, especially if a switch in TKI treatment is being considered. FFPE tumor tissue will be subjected to central NGS-based multiplex analysis. Central NGS-based analysis of baseline FFPE biopsies is mandatory for participation in this trial. • Blood samples are taken at baseline (i.e., up to 7 days prior to first administration of study medication, D1-7 days) and with every radiologic assessment with CT/MRI during 1st- and 2nd-line treatment (i.e. two cycles [8 weeks] after start of a new ALK inhibitor, and every 12 weeks [Q12W ±7 days] during continuation of treatment, i.e. at the same time as imaging studies are performed). Analyses will include: • Correlation of systemic and brain efficacy with molecular markers, such as the *ALK* fusion variant and *TP53* status. • Correlation of resistance mechanisms with the compounds used and with molecular markers, such as the *ALK* fusion variant and *TP53* status. • Correlation of site of progression with molecular markers, such as the *ALK* fusion variant and *TP53* status.
RATIONALE	Currently, in Germany several TKI are approved for the treatment of ALK+ NSCLC. Taking advantage of (1) the authorization status and rapid penetration of 2nd-generation ALK TKI in 1st-line treatment in Germany, (2) the broad availability of NGS-based molecular testing for primary biopsies

	and rebiopsies within the German national Network on Genomic Medicine in Lung Cancer (nNGM), and (3) the trial network available in the German IIT context, this phase II trial is conducted with the aim to generate hypotheses regarding the following key questions: a) Is there an optimal upfront treatment among currently available TKI? b) Are there particular resistance patterns associated with each compound? c) What is the additional effect of *ALK* variant status and *TP53* mutations on patterns of acquired resistance, i.e. are there particular compound-specific properties indicating superiority according to the type of *ALK* variant? d) Are there differences in brain control according to the upfront treatment? e) Might exploration of ctDNA (liquid biopsies) improve monitoring of disease and guidance of treatment (assessing resistance mutations, proxys of epithelial-mesenchymal transition [EMT] etc.)? f) Might analysis of cerebrospinal fluid in the same way support clinical decisions (guidance of next-line TKI treatment) in case of "brain-only" progression? In this phase II trial, ALK$^+$ patients are randomized into two arms. The experimental Arm B comprises sequential treatment with brigatinib in 1st line followed by 2nd-line treatment with any ALK TKI according to investigator's choice. In the standard Arm A, patients are treated with any 2nd-generation TKI except for brigatinib in 1st line (currently alectinib or ceritinib) according to investigator's choice, followed by 2nd-line treatment with any ALK TKI also according to physician's choice (see Figure 2). The choice of comparator 2nd-generation TKI in the 1st-line setting as well as the TKI used in 2nd-line treatment is up to the investigator and the latter should ideally take into account mechanisms of acquired resistance (i.e. ALK resistance mutations) as detected by repeat tissue or liquid biopsies at the time of disease progression. If considered appropriate by the treating physician, patients enrolled in Arm A will also be offered the possibility of treatment with brigatinib in the 2nd line, which will be provided by Takeda. Detailed clinical annotation as well as collection of tumor tissue and blood samples for subsequent comprehensive molecular characterization are pivotal in this study. By analyzing the relationship of clinical and molecular parameters with ALK TKI efficacy, as captured by the primary and secondary endpoints of the trial, the data gathered will help optimize treatment of ALK$^+$ NSCLC patients and define the most advantageous position of brigatinib in the treatment scenario of this entity.
INCLUSION CRITERIA	1. Fully informed written consent and any locally-required authorization (EU Data Privacy Directive) given by the patient 2. Male or female ≥ 18 years of age NOTE: There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. Histologically confirmed locally advanced (stage III) and not suitable for curative treatment, i.e. R0 operation or definitive chemo-/radiation, or metastatic (stage IV) ALK$^+$ NSCLC NOTE: Documentation of ALK rearrangement by a positive result of any ALK assay approved in Germany [i.e. positivity for at least one of the three: immunohistochemistry (IHC), NGS, fluorescence *in situ* hybridisation (FISH)] must be available at baseline. Treatment can already be started based on a local ALK$^+$ test result, but subsequent central testing of the baseline biopsy for molecular profiling, incl. determination of *ALK* variant and *TP53* status, should be made possible for all patients. 4. No prior therapy for metastatic ALK$^+$ NSCLC including therapy with ALK inhibitors. However, 1 or 2 cycles of chemotherapy as well as cerebral irradiation before inclusion in the study will be allowed.

	5. At least 1 measurable (i.e., target) lesion per RECIST v1.1 6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 7. Have adequate organ function, as determined by: • Total bilirubin ≤1.5x the upper limit of the normal range (ULN) (< 3x the ULN if Gilbert's disease is present) • Estimated glomerular filtration rate ≥30 mL/minute/1.73 m^2 (calculated by MDRD or any other validated formula, see Appendix 13.4) • Alanine aminotransferase/aspartate aminotransferase ≤2.5x ULN NOTE: ≤5x ULN is acceptable if liver metastases are present. • Serum lipase ≤1.5x ULN • Platelet count ≥75x 10^9/L • Hemoglobin ≥9 g/dL • Absolute neutrophil count ≥1.5x 10^9/L 8. Willingness and ability to comply with scheduled visit and study procedures 9. Patient willing to participate in accompanying research program 10. Collection of current biopsy during screening must be feasible NOTE: For each patient a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be available for biomarker evaluation. Excisional, incisional or core needle biopsies are appropriate, while fine needle aspirations are insufficient. 11. Women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days prior to randomization. Women must not be breastfeeding. 12. Female patients who: - are postmenopausal for at least 1 year before the screening visit, OR - are surgically sterile, OR - if they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through *4 months* after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. Male patients, even if surgically sterilized (i.e., status post-vasectomy), who: - agree to practice effective barrier contraception during the entire study treatment period and through *4 months* after the last dose of study drug, OR - agree to completely abstain from heterosexual intercourse.
EXCLUSION CRITERIA	1. History or presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis 2. Uncontrolled hypertension (patients with hypertension have to be under adequate treatment for control of blood pressure upon study entry) 3. Systemic treatment with stro ng cytochrome P-450 (CYP) 3A inhibitors, strong CYP3A inducers, or moderate CYP3A inducers or treatment with any investigational systemic anticancer agents, chemotherapy or radiation therapy (except for stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days of randomization 4. Treatment with antineoplastic monoclonal antibodies within 30 days of randomization 5. Major surgery within 30 days of randomization. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed. 6. Current spinal cord compression (symptomatic or asymptomatic) as detected by radiographic imaging. Patients with leptomeningeal disease without cord compression are allowed.

	7. Significant or uncontrolled cardiovascular disease, specifically including, but not restricted to the following: • If an acute coronary syndrome has ensued in the past 6 months, successful reperfusion has to be documented and the patient has to be free of symptoms. • New York Heart Association Class III or IV heart failure within 6 months prior to randomization • Any history of clinically significant ventricular arrhythmia 8. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug 9. Malabsorption syndrome or other gastrointestinal illness or condition that could affect oral absorption of the study drug 10. Active severe or uncontrolled chronic infection, including but not limited to, the requirement for intravenous antibiotics for longer than 2 weeks 11. History of HIV infection. Testing is not required in the absence of history. 12. Chronic hepatitis B (surface antigen-positive) or chronic active hepatitis C infection. Testing is not required in the absence of history. 13. Any serious medical condition or psychiatric illness that could, in the investigator's opinion, potentially compromise patient safety or interfere with the completion of treatment according to this protocol 14. Known or suspected hypersensitivity to brigatinib or other TKI or their excipients 15. Life-threatening illness unrelated to cancer 16. Involvement in the planning and/or conduct of the study (applies to both Takeda staff and/or staff of sponsor and study site) 17. Patient who might be dependent on the sponsor, site or the investigator 18. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities [§ 40 Abs. 1 S. 3 Nr. 4 AMG] 19. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG] 20. Legal incapacity or limited legal capacity 21. Females who are pregnant or breastfeeding 22. Patients who have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days prior to randomization. NOTE: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for 7 days prior to randomization.

STUDY TREATMENT SCHEDULE	1st-line treatment: In the standard arm (Arm A) patients will receive any approved 2nd-generation TKI (currently alectinib or ceritinib) according to investigator's choice. In the experimental arm (Arm B) patients will receive • 90 mg brigatinib QD p.o. for the first 7 days (lead-in) followed by • 180 mg brigatinib QD p.o. afterwards, starting with day 8. 2nd-line treatment: In both arms, patients will receive any available ALK TKI according to investigator's choice. Initiation of medication intake will take place after an obligatory washout period of 3 days between the 1st and 2nd line treatment (based on the half-lives of second-generation ALK TKI and in order to allow for a drop in the plasma concentration of the 1st-line TKI to <30%), while treating physicians will also consider additional potentially relevant factors, for example the need to wait even longer for resolution of any previous toxicity. The choice of TKI used in 2nd-line should ideally take into account mechanisms of acquired resistance (i.e. ALK resistance mutations) as detected by repeat tissue or liquid biopsies at the time of disease progression. If considered appropriate by the treating physicians, patients enrolled in Arm A will be offered the possibility of treatment with brigatinib in the 2nd line in the dosage described for the 1st-line experimental Arm B (90 mg brigatinib QD p.o. for the first 7 days of 2nd line [lead-in] followed by 180 mg brigatinib QD p.o. starting with day 8), which will be provided by Takeda.
DURATION OF STUDY TREATMENT	Subjects will continue to be treated with brigatinib or other TKI as long as they derive clinical benefit as determined by the treating physicians (this can include treatment beyond progression per RECIST v1.1 criteria in some cases with oligo-progression and ongoing clinical benefit) or until intolerable toxicity, patient's request to discontinue treatment, or another discontinuation criterion is met. Treatment duration in 1st and 2nd line is not limited to a certain timeframe and will continue until one of the above-mentioned criteria is met.
EFFICACY EVALUATIONS / CRITERIA	CT/MRI with contrast (unless use of contrast media is contraindicated) imaging of chest and abdomen incl. adrenal glands will be performed for all patients. Tumor response is determined based on the Response Evaluation Criteria in Solid Tumors (RECIST v1.1; Eisenhauer et al., 2009; investigator assessment). Baseline tumor evaluation will be performed at screening. Response assessment is recommended according to the standard of care, which should be after two cycles (8 weeks) of treatment in the 1st and 2nd line, and afterwards every 12 weeks (Q12W ±7 days) during active 1st-and 2nd-line treatment, respectively. For 2nd-line treatment, baseline disease assessment should be performed within 30 days prior to start of 2nd-line treatment. Intracranial response evaluation is performed based on RECIST v1.1 criteria. Contrast-enhanced MRI/CT of the brain will be performed at screening for all patients. Due to the higher sensitivity, use of MRI is strongly recommended. In case of brain metastases at baseline as well as in every case of cerebral progression at any later time-point, brain imaging (preferably with MRI) is recommended according to the standard of care, which should be at the time of next scheduled assessment (i.e., 8 weeks after beginning of 1st or 2nd line, and 12 weeks after any other restaging). Thereafter, further brain imaging (preferably with MRI) is recommended every 12 weeks (Q12W ±7 days) during active treatment in the 1st and 2nd line, respectively. In addition, it is recommended to adapt brain imaging intervals according to the location and size of metastases, for example lesions with large size or critical location (e.g. infratentorial) might require more frequent monitoring. For patients without brain lesions in baseline testing, surveillance imaging is recommended according to the same scheme, i.e. an MRI of the brain is recommended at every second time-point of radiologic assessment (that is 20 weeks after beginning of 1st or 2nd line, and every 24 weeks thereafter) in order to facilitate

	early detection of newly-developed brain lesions that will potentially be amenable to local ablative treatment. After study treatment discontinuation for reasons other than progressive disease, imaging of chest and abdomen incl. adrenal glands is recommended to be performed every 12 weeks (Q12W ±21 days), while imaging of brain is recommended to be performed every 24 weeks (Q24W ±21 days) until progression, death or initiation of another anti-cancer therapy according to standard of care (SOC).
SAFETY EVALUATIONS	Safety assessments will include physical and laboratory examinations, vital signs, performance status, and electrocardiograms. All observed toxicities and side effects will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE, version 4.03) for all patients, and the potential association of each with the study treatment assessed and summarized. Treatment-related serious adverse events rate (SAE) will be determined. AEs and toxicities are assessed on day 1 of every cycle during study treatment and in the safety follow-up.
STATISTICAL METHODS	This is an exploratory phase II trial aiming to generate hypotheses for future trials. Hence, the sample size of n=116 is primarily determined by considerations of feasibility and costs. Besides, in order to plan the duration of the trial, an estimation regarding the expected median PFS of the 1st-line treatment in the two treatment arms is important, but poses a special challenge: recently published interim results from the ongoing phase 3 ALTA-1L (Camidge 2018c) and ALEX (Camidge 2018d, Peters 2017) trials show that the PFS curve of ALK^{+} NSCLC patients receiving 1st-line brigatinib or alectinib, respectively, vs. crizotinib, forms a plateau at the level of about 50%, which causes the observed median PFS times to be a relatively “unstable” measure of treatment efficacy. In contrast, hazard ratios (HR) are generally more robust effect estimates than median PFS times, since they take into account the entire PFS curves under comparison instead of relying on a single time point. For example, the observed median PFS for alectinib was 25.7 months as assessed by the independent radiology review committee of the ALEX trial in 2017 with a HR=0.5 vs. crizotinib (Peters 2017), but “jumped” to 34.8 months (35% change) despite a much smaller HR change to 0.43 (14% change) in this year’s investigator-assessed-only update (Camidge 2018d). On the other hand, the median PFS under crizotinib was reported by the investigators as 11.1 months in the first ALEX report (Peters 2017) and 10.9 months in this year’s update (Camidge 2018d), i.e. appears to be relatively robust, because it is much shorter and the PFS curves for crizotinib are quite steep at the level of 50%. Therefore, for statistical calculations regarding the ABP trial, we decided to consider the more robust HR of brigatinib and alectinib vs. crizotinib in the ALTA-1L and ALEX studies, together with the more “stable” median estimate of crizotinib PFS, rather than the directly observed, but more “variable” median PFS of alectinib and brigatinib themselves. Aim was to delineate the follow-up times necessary for 1st- and 2nd-line treatment as well as to assess the expected 95% confidence interval (CI) range in the determination of PFS1 as a first exploratory parameter. For these calculations, the HR for PFS of 1st-line alectinib vs. crizotinib was considered 0.45 (the average of the 0.47 and 0.43 as assessed by the investigators in the 2017 and 2018 interim analyses [Peters 2017, Camidge 2018d]), the HR for PFS of 1st-line brigatinib vs. crizotinib was assumed identical to that of 1st-line alectinib vs. crizotinib (based on the very similar observed HR=0.49 (95% CI 0.33-0.74) in the ALTA-1L trial [Camidge 2018c]), and the median PFS under 1st-line crizotinib treatment was considered to be 11 months (i.e. the average of 11.1 and 10.9 months observed by the investigators in the 2017 and 2018 interim analyses of the ALEX trial [Peters 2017, Camidge 2018d]). Consequently, assuming an exponential distribution of PFS, the expected median PFS under 1st-line alectinib treatment was

	considered to be 24.4 months (11/0.45), and the duration of the ABP trial is proposed based on a follow-up time of 32 months for the last patient, which considers an expected PFS of 24.4 months under 1st treatment plus an expected PFS of about 7 months under 2nd line treatment with a different ALK inhibitor (based on the median PFS of 5.5-6.9 (95% CI 2.9-9.5) months observed with lorlatinib after failure of second-generation ALK inhibitors in the EXP3B/4/5 cohorts of a phase 2 trial [Solomon 2017]). The accrual of the trial is proposed as 36 months based on the expected number of newly-diagnosed ALK^+ patients in the centers expected to participate. In order to quantify the potential degree of evidence regarding PFS1 that can be gained with a number of n=116 patients at hand, we calculated the number of expected events *d*, the expected 95% CI for the median PFS of alectinib and brigatinib in the 1st line (assumed to be equal, as explained above), and the expected 95% CI for the HR of PFS under 1st-line brigatinib vs. alectinib in the ABP trial (assumed to be 1, as explained above), given a constant accrual over a time of 36 months, a follow-up time of 32 months for the last patient, and exponentially distributed PFS times. Under these assumptions, the expected number of PFS events is *d*=87, the expected 95% CI of the median PFS in the 1st line is [16.6 – 34.2 months] (both arms), and the expected 95% CI of the HR for PFS in the 1st line [0.66 – 1.52]. The number of events *d* was calculated using the formula by Schoenfeld (Schoenfeld 1981) and the software ADDPLAN v6.1, the confidence interval calculation for the median PFS was done via bootstrapping using 1,000,000 datasets simulated in R v3.3.3 (http://r-project.org) and a fixed random number seed to yield stable and reproducible results, and the confidence interval for the HR was calculated using the (approximate) formula $\exp(\pm 1.96\sqrt{4/d})$ (Wassmer 2006). A Cox proportional hazards model will be used to assess the primary endpoint PFS. As covariates, the model includes the factor “treatment group” and is adjusted for the presence of brain metastases at baseline (yes vs. no) and ECOG (0-1 vs. 2). The treatment groups will be compared at a two-sided α of 0.05, and 95% confidence interval for the hazard ratio will be given. Furthermore, Kaplan-Meier curves will be provided. Primary analysis will be based on the ITT population including all randomized patients. Sensitivity analyses will be conducted for the per-protocol set (patients without major protocol violations) and for predefined subgroups. Analyses of secondary endpoints will be descriptive and will include the calculation of appropriate summary measures of the empirical distributions. For the analysis of Adverse Events, summary tables will be generated for the incidence of AEs overall and by severity. This will also be done for Serious Adverse Events. The AE summary tables will provide the number and percentage of patients with adverse events and the 95% confidence intervals for the event rates.	
INDIVIDUAL STUDY DURATION PER SUBJECT	Subjects who discontinue 1st- or 2nd-line treatment for reasons other than progressive disease will continue to have surveillance imaging until progression, death or initiation of another anti-cancer therapy according to the standard of care. Thereafter, following disease progression, survival follow-up visits will be performed by phone contact or office visit until end of study (EOS).	
PLANNED TRIAL PERIOD	Planned first patient first visit (FPFV)	Approximately Q4 2019
	Last patient first visit (LPFV)	FPFV + 36 months Approximately Q4 2022
	Last patient last visit (LPLV = EOS)	LPFV + 32 months Approximately Q3 2025