Clinical trial proposal

ERAZER

An open-label, multicenter phase II trial of amivantamab and chemotherapy induction and amivantamab, lazertinib and bevacizumab maintenance in patients with advanced or metastatic *EGFR*-mutant non-small cell lung cancer

Sponsor:	University of Cologne
Principal Investigator (PI):	Sebastian Michels
Authorship:	Lung Cancer Group Cologne
Trial protocol code:	TBD
EudraCT number:	TBD
Version:	V4.1.1
Release:	August 19th 2021

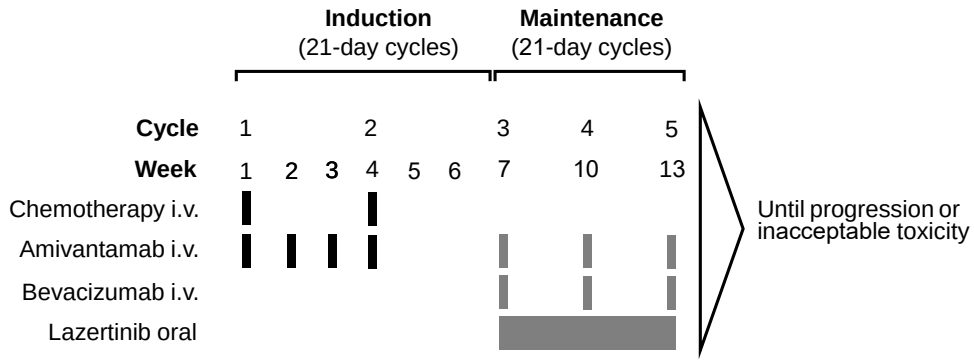
1. Synopsis

1. General considerations	
1.1 Principal Investigator	PI: Sebastian Michels, MD Lung Cancer Group Cologne, Dept. I of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne Co-PI: Prof. Jürgen Wolf, MD Lung Cancer Group Cologne, Dept. I of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne
1.2 Study sponsor	University of Cologne, Albertus-Magnus-Platz, 50923 Cologne, Germany Represented by: Lung Cancer Group Cologne, Dept. I of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne
1.3 Study drugs	Lazertinib Amivantamab (JNJ-61186372) Bevacizumab Pemetrexed Carboplatin
1.4 Primary indication	Patients with advanced non-small cell lung cancer harbouring sensitizing *EGFR* mutations after failure of treatment with osimertinib
1.5 Overview of the trial design	Proof-of-concept, open label, single arm, multicenter, phase II trial including a safety run-in part
2. Specific considerations	
2.1 Short summary of the trial rational and primary hypothesis	Osimertinib treatment is standard-of-care in the first line setting in *EGFR*-mutant lung cancer. However, resistance inevitably develops after a median progression free survival (PFS) of about 18 months. At that stage, the genetic heterogeneity is high and a multitude of molecular mechanism of resistance may occur. However, *MET* amplification and secondary *EGFR* mutation constitute the largest subset (~30%). Disease control by treatments aiming at suppressing detected mechanism of resistance is short lasting and currently only chemotherapy combined with the VEGF antibody bevacizumab and the PD-L1 antibody atezolizumab result in moderate but clinically meaningful progression-free survival times. The current understanding is, that the pronounced genetic heterogeneity builds the basis for a rapid outgrowth of other mechanisms of resistance. Thus, there is a high unmet clinical need for more effective treatments in the setting of osimertinib resistance. A strategy combining drugs that target a specific mechanism of resistance and drugs that target genetic heterogeneity independently from the underlying genotype may enhance treatment efficacy and prolong the development of resistance and progression. The combination of an induction treatment with the EGFR-MET bispecific antibody amivantamab and chemotherapy followed by a maintenance treatment of the EGFR inhibitor lazertinib, amivantamab and the VEGF antibody bevacizumab would fulfil these requirements.

2.2 Detailed trial rationale and primary hypothesis	Lung cancer is the second most common malignancy in males and females and the leading cause of cancer-related death in the Western world. With a median of 7 to 8 months, overall survival (OS) with conventional chemotherapy in the metastatic stage was short until just recently *(Schiller et al., N Engl J Med 2002)*. Since the discovery of an increasing number of activating genetic aberrations in driver oncogenes, lung cancer is commonly classified based on its genomic background. Activating mutations in the *Epidermal Growth Factor Receptor* (*EGFR*) are found in 10% to 15% of Western adenocarcinoma patients *(CLCGP and NGM, Sci Transl Med 2013; The Cancer Genome Atlas Research Network, Nature 2014)*. These result in the constitutive activation of the kinase and the recruitment of oncogenic downstream signalling pathways. Unlike most lung cancers, *EGFR*-mutant disease may not be associated with cigarette smoking or other carcinogens and may therefore also affect individuals of young age. EGFR tyrosine kinase inhibitors (TKIs) are highly effective in patients with *EGFR*-mutant lung cancer and have become standard-of-care in first line. Based on the mode of action and the mutation-specificity, EGFR TKIs are classified into first- (erlotinib, gefitinib), second- (dacomitinib, afatinib) and third-generation (osimertinib, lazertinib) inhibitors. EGFR inhibitors used in first-line have led to a substantial prolongation of PFS) compared to chemotherapy *(Rosell et al., Lancet 2012; Park et al., Lancet 2016; Wu et al., Lancet Oncol 2017; Mok et al., N Engl J Med 2017)*. Based on the significant prolongation of PFS (18.9 months; 95% CI, 15.2-21.4) and OS (38.6 months; 95% CI, 34.5-41.8) as compared to upfront treatment with first-generation inhibitors, treatment with the third-generation EGFR inhibitor osimertinib has become standard-of-care in treatment-naïve patients in most countries *(Soria et al., N Engl J Med 2018; Ramalingam et al. N Engl J Med 2019)*. Despite these significant improvements, resistance to third-generation inhibitors inevitably develops through the acquisition of molecular aberrations. Genetic heterogeneity is significantly increased upon treatment with third-generation inhibitors, resulting in a multitude of different resistance-mediating factors (*Blakely et al. Nat Genet 2017; Michels et al. JCO Precis Oncol 2019; Oxnard et al. JAMA Oncol 2018; Piotrowska et al. Cancer Discov 2018*). Among these aberrations, amplifications of *MET* and secondary mutations in *EGFR* occur most frequently and constitute a subgroup of more than 30% of patients. Despite the fact, that *MET* amplification for instance is targetable by combining MET inhibitors with EGFR inhibitors, response rates and PFS times in patients who previously received a third-generation EGFR inhibitor remain below the expectations - ORR 30% and median PFS 5.4 months (*Sequist et al. Lancet Oncol 2020*). Another approach is the combination of the third-generation EGFR inhibitor lazertinib and the EGFR-MET bispecific antibody amivantamab that target *MET*- and *EGFR*-mediated resistance at the same time. Still, the response rate remains below 50% (*Cho et al. Ann Oncol 2020*). However, activity was also seen in patients whose tumors did not harbour *EGFR*- or *MET*-based resistance, indicating the high potential of the compound. Currently, the most effective approach for patients with progression to osimertinib is treatment with platinum-based chemotherapy, bevacizumab and the PD-L1 antibody atezolizumab (IMpower150 regimen). This quadruple combination resulted in a median PFS of 9.7 months in patients who previously received EGFR inhibitors (*Reck et al. Lancet Resp Med 2020*). But, from our own experience, one major limitation of this regimen is the high rate of central nervous system (CNS)

	progression, including leptomeningeal tumor spread due to the lack of a drug with sufficient CNS activity. It is commonly thought that the high degree of intratumor heterogeneity that is boosted by targeted treatments and especially by third-generation EGFR inhibitors compromises long lasting responses. Therefore the combination of agents that specifically target specific mechanism of resistance, combined with drugs that target genetic heterogeneity (e.g. chemotherapy) may be more effective than each regimen on its own. Additionally, we hypothesize that applying a drug with CNS activity such as osimertinib or lazertinib may postpone CNS relapse.
2.3 Rational for regimen selection	Just recently, two randomized trials were published, that investigated the combination of EGFR TKI treatment with platinum-based chemotherapy in the first line. These combinations resulted in a significant prolongation of PFS and OS by about 8 months and 12 months, respectively, as compared to the EGFR TKI alone *(Hosomi et al., J Clin Oncol 2019; Noronha et al., J Clin Oncol 2019)*. As mentioned above, these effects may in part be attributed to the reduction in tumor heterogeneity by the chemotherapy agents. Trials investigating osimertinib in combination with chemotherapy have recently started recruiting (NCT04035486). Similarly, the combination of VEGF- or VEGFR-targeting antibodies with the EGFR inhibitor erlotinib achieved significant prolongation of PFS with a reasonable safety profile (*Reck et al., Lancet Oncol 2019*). Based on the data recently published, the third-generation EGFR inhibitor lazertinib seems to be as efficacious as osimertinib *(Ahn et al., Lancet Oncol 2019)*. The bispecific EGFR-MET antibody amivantamab (JNJ-61186372) has shown single agent activity in patients with *EGFR*-mutant lung cancer that have acquired resistance to osimertinib by secondary *EGFR* mutations or *MET* amplification as well as other aberrations *(Haura et al., J Clin Oncol 2019)*. Apart from direct action on the mechanisms of resistance, amivantamab also promotes antibody-dependent antitumor immune response. In an ongoing phase I trial that investigates treatment with amivantamab and lazertinib data of the first 71 patients was recently reported (*Cho et al., Ann Oncol 2020*). This combination resulted in confirmed complete and partial responses in 6 out of 20 patients. Additionally, a phase I trial (Chrysalis; NCT04538664) and a large phase III trial (Papillon; NCT04538664) currently investigate the combination of amivantamab plus platinum-based doublet chemotherapy in *EGFR* ex20ins-positive NSCLC. Data on the safety and efficacy of this combination has not been published yet. In summary, the combination treatment of EGFR-targeting agents with platinum-based chemotherapy, VEGF- or VEGFR-antibodies or the bispecific EGFR-MET antibody amivantamab turned out to be safe and tolerable (see 2.4 for further information). Additionally, treatment intensification by combining these agents resulted in enhanced efficacy as compared to EGFR-directed monotherapy. Therefore, we believe, that the combination of amivantamab and chemotherapy as induction treatment followed by the combination of amivantamab, lazertinib and bevacizumab as maintenance treatment may be safe, tolerable and more efficacious than the current standard-of-care in patients with *EGFR*-mutant NSCLC who have progressed on osimertinib treatment.

2.4 Safety considerations and risk-benefit assessment	2.3.1 Safety considerations The combination of gefitinib, pemetrexed and carboplatin were investigated in two randomized trials *(Hosomi et al., J Clin Oncol 2019; Noronha et al., J Clin Oncol 2019)*. Patients received four cycles of pemetrexed (500 mg/m2) and carboplatin (AUC 5) every three weeks and a continuous treatment with gefitinib (250 mg QD). Safety and efficacy were assessed in 346 patients in total. Grade 3 adverse events (AEs) occurred up twice as often in the chemotherapy combination. However, the vast majority of Grade 3 AEs were due to diverse cytopenia, which was attributed to chemotherapy. No unexpected or excessive toxicity was reported in either of the trials. Similarly, the combination of erlotinib and the VEGF-targeting antibody bevacizumab and the VEGFR-targeting antibody ramucirumab has been evaluated in several clinical trials and toxicity was shown to be manageable. Treatment with lazertinib is well tolerated and resulted in very few high-grade EGFR TKI-specific adverse effects. In view of the safety profile, we believe that lazertinib is comparable to osimertinib *(Ahn et al., Lancet Oncol 2019)*. Amivantamab has shown promising results as monotherapy in patients who have progressed while on treatment with osimertinib, breaking resistance mediated by secondary EGFR mutations or MET amplification. Treatment was generally well tolerated with mild infusion-related reactions being most frequent (61% overall frequency). Additionally, EGFR inhibition-specific treatment-emergent AEs were recorded in the majority of patients (e.g. rash, up to 64%; paronychia, up to 33%; interstitial lung disease 1-5%). No hematologic toxicity was observed. A trial investigating the safety of the combination of lazertinib and amivantamab is being conducted (*Cho et al., Ann Oncol 2020*). So far, no excessive toxicity has been reported and ≥ Grade 3 AEs were reported in 7% of patients only. The majority of AEs were restricted to those that are typically associated with EGFR-inhibition, such as low grade rash (78%) and paronychia (42%). The incidence of infusion-related reactions remained around 60%. Additionally, a phase I trial (Chrysalis; NCT04538664) and a large phase III trial (Papillon; NCT04538664) currently investigate the combination of amivantamab plus platinum-based doublet chemotherapy in EGFR ex20-positive NSCLC. Data on the safety and efficacy of this combination has not been published yet. However, no synergistic toxicity may be expected from this combination. Based on these findings, we believe that a treatment regimen combining an induction part of amivantamab, carboplatin and pemetrexed and a maintenance part with amivantamab, lazertinib and bevacizumab is tolerable with a manageable safety and toxicity profile. 2.3.2 Risk-benefit assessment No recommended-phase-2-dose (RP2D) has yet been established for the combination of amivantamab, lazertinib and bevacizumab. Data on the safety and tolerability of amivantamab plus chemotherapy has not been published yet. But, as outlined above, no unexpected or excessive toxicity was reported for similar drug combinations and treatment approaches. As this trial starts, the safety of the induction part with amivantamab and chemotherapy will have been extensively explored in a large phase I and phase III trial. Therefore, no safety run-in part will be necessary for the induction regimen. In order to establish the RP2D for the maintenance regimen, a safety run-in part will be preceding the main trial part.

	Since metastatic lung cancer is inevitably deadly, the benefits probably exceed the risks of the treatment. Nevertheless, it may be discussed whether treatment with single drugs may be scheduled or dose modified during the induction phase. Meaning, that one drug is administered later during treatment or temporarily at a reduced dose.
2.5 Treatment regimen and dose levels for safety run-in	*2.5.1 Induction part regimen (C1 and C2)* Induction treatment will be administered for two cycles (21-day cycles) Amivantamab (JNJ-61186372) 1,750 mg (≥80 kg body weight) or 1,400 mg (<80kg body weight) i.v. Q1W starting at C1D1 up to C2D1 or until progression or inacceptable toxicity Pemetrexed 500 mg/m2 body surface i.v. Q3W starting at C1D1 for 2 cycles as induction or until progression or inacceptable toxicity Carboplatin AUC5 Q3W i.v. starting at C1D1 for up to 4 cycles or until progression or inacceptable toxicity *2.5.2. Maintenance part regimen (C3 ongoing)* Maintenance treatment will be administered from cycle three ongoing (21-day cycles) Amivantamab (JNJ-61186372) 2,100 mg (≥80 kg body weight) or 1,750 mg (<80 kg body weight) i.v. Q3W starting at C3D1 until progression or inacceptable toxicity Lazertinib 240 mg QD orally starting at C3D1 until progression or inacceptable toxicity Bevacizumab i.v. Q3W at the RP2D starting at C3D1 until progression or inacceptable toxicity  *Figure 1. Schematic treatment plan*

2.5.3 Dose levels for the maintenance regimen in the safety run-in part

Dose level	Lazertinib daily dose QD	Amivantamab dose Q3W	Bevacizumab dose Q3W
1	240 mg	2,100 mg (≥80 kg) 1,750 mg (<80 kg)	15 mg/kg
-1	240 mg	2,100 mg (≥80 kg) 1,750 mg (<80 kg)	tbd

2.6 Trial design

Open label, single arm, multicenter phase II trial including a safety run-in part

This phase II trial will be split in two parts:

1. A **safety run-in part** investigating the treatment regimen in 6 to 12 patients (*see Figure 1*) to determine the RP2D of the maintenance treatment with amivantamab, lazertinib and bevacizumab (safety run-in endpoint)
2. A **main trial part** to determine the main trial endpoints

The trial will be conducted within the national Network Genomic Medicine (NGM) and in collaboration with the Arbeitsgemeinschaft Internistische Onkologie (AIO). In total up to 15 trial sites will be opened for recruitment.

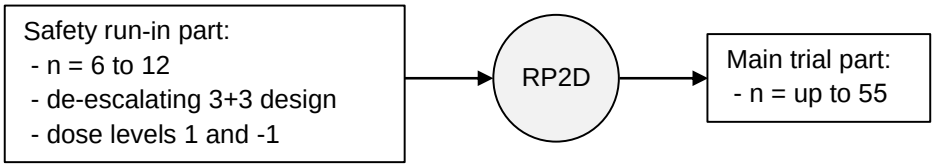


Figure 2. Trial design

2.7 Summary of trial procedures

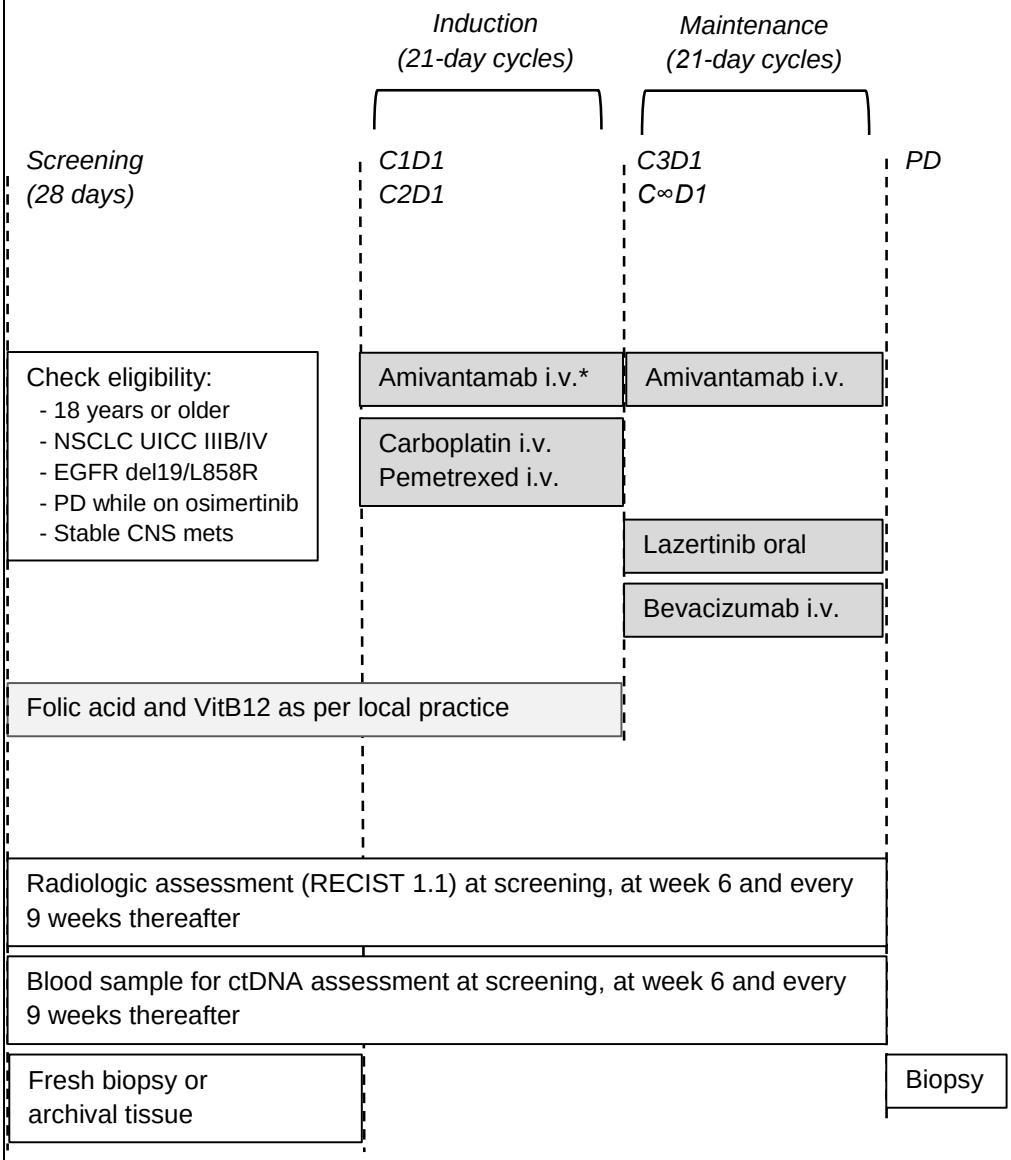


*Figure 3. Flow chart of trial procedures.*Q1W dosing during C1*

Patients, over 18 years of age who are diagnosed with an *EGFR* mutation-positive (*EGFR* del19 or *EGFR* L858R) advanced/inoperable or metastatic (UICC IIIB, IIIC or IV) non-small cell lung cancer may be screened for participation in this trial after failure of osimertinib in the first line or adjuvant setting. A rebiopsy prior to treatment is mandatory. Patients may participate independently from the detected mechanism of resistance. Screening for *EGFR* mutation status and other genetic aberrations will be performed locally for eligibility assessment. Tissue samples will be sent in for central validation and secondary endpoint assessment. During screening, patients will receive an adequate baseline quantification of the disease status including an MRI of the brain. Patients with CNS metastases may participate as long as they do not require increasing doses of steroids, local ablative therapy or have carcinomatous meningeosis.

In the safety run-in part, patients will be treated at the designated dose level. The DLT period comprises the first two cycles of the maintenance regimen (lazertinib, amivantamab and bevacizumab). Though, no drug-drug interaction may be

anticipated, pharmocokinetic (PK) analyses will be performed for scientific reasons. Blood samples for PK analyses will be collected during the maintenance part.

Patients who participate in the main trial part will be treated at the RP2D.

Treatment will be administered as outlined in *Figure 1* and in *Section 2.5.*. Treatment will be split in an induction part and a maintenance part, both administered in 21-day cycles until progression, inacceptable toxicity, withdrawal of the informed consent or at the discretion of the investigator.

Patients will be followed for efficacy by CT of the thorax, the abdomen and pelvis as well as by MRIs of the brain after the first 6 weeks and every 9 weeks thereafter. Scans will be evaluated according to RECIST v1.1 for all efficacy endpoints.

At baseline, throughout treatment and at progression, blood samples will be collected for ctDNA analysis.

Additionally, a tissue biopsy may optionally be collected at progression to investigate molecular mechanisms of resistance. Preferentially, this biopsy will be snap frozen and sent on dry ice for further molecular analyses including DNA and RNA next-generation sequencing and transciptomic analyses.

2.8 Estimated number of visits and i.v. drug applications

2.8.1 Safety run-in trial part - Estimated number of study visits, assuming a median PFS of 14 months (19 cycles)

	Number of visits	Cumulative number of visits
Screening	1	1
Cycle 1 (induction; 21-day)	4	5
Cycle 2 (induction; 21-day)	3	8
Cycle 3 (maintenance; 21-day)	3	11
Cycle 4 (maintenance; 21-day)	3	14
≥ Cycle 5 (maintenance; 21-day)	15	29
EOT	1	30
Unscheduled	4	34

2.8.2 Main trial part - Estimated number of study visits, assuming a median PFS of 14 months (19 cycles)

	Number of visits	Cumulative number of visits
Screening	1	1
Cycle 1 (induction; 21-day)	4	5
Cycle 2 (induction; 21-day)	2	7
Cycle 3 (maintenance; 21-day)	2	9
Cycle 4 (maintenance; 21-day)	2	11
≥ Cycle 5 (maintenance; 21-day)	15	26
EOT	1	27
Unscheduled	4	31

<table>
<tr><td></td><td><u>2.8.3 Total number of visits, estimating 12 patients to be enrolled in the safety-run-in part</u>

(Safety run-in) 12 x 34 = 408 visits

(Main trial) 43 x 31 = 1,333 visits

Total = 1,741 visits

<u>2.8.4 Estimated number of i.v. applications for each drug</u>

<table><tr><th>Drug</th><th>Number of i.v. applications</th></tr><tr><td>Amivantamab</td><td>22</td></tr><tr><td>Bevacizumab</td><td>17</td></tr><tr><td>Pemetrexed</td><td>2</td></tr><tr><td>Carboplatin</td><td>2</td></tr><tr><td>Total</td><td>43</td></tr></table></td></tr>
<tr><td colspan="2">3. Objectives, endpoints and statistical considerations</td></tr>
<tr><td>3.1 Primary objective</td><td>1. Safety run-in part: To determine the RP2D for the maintenance treatment regimen (amivantamab, lazertinib and bevacizumab)

2. Main trial part: To determine the efficacy of the trial treatment.</td></tr>
<tr><td>3.2 Primary endpoint</td><td>1. Safety run-in part: Dose-limiting toxicities in patients treated at defined dose levels

2. Main trial part: PFS according to RECIST v1.1 by local investigator assessment</td></tr>
<tr><td>3.3 Secondary objectives</td><td>1. Safety run-in part: To characterize the PK of the experimental treatment

2. Both parts: To assess additional efficacy objectives

3. Both parts: To characterize the safety and tolerability

4. Both parts: To assess efficacy objectives in pre-specified patient subgroups (i.e. patients with brain metastases)</td></tr>
<tr><td>3.4 Secondary endpoints</td><td>1. Safety run-in part: Plasma concentration vs time profiles - plasma PK parameters of the experimental treatment

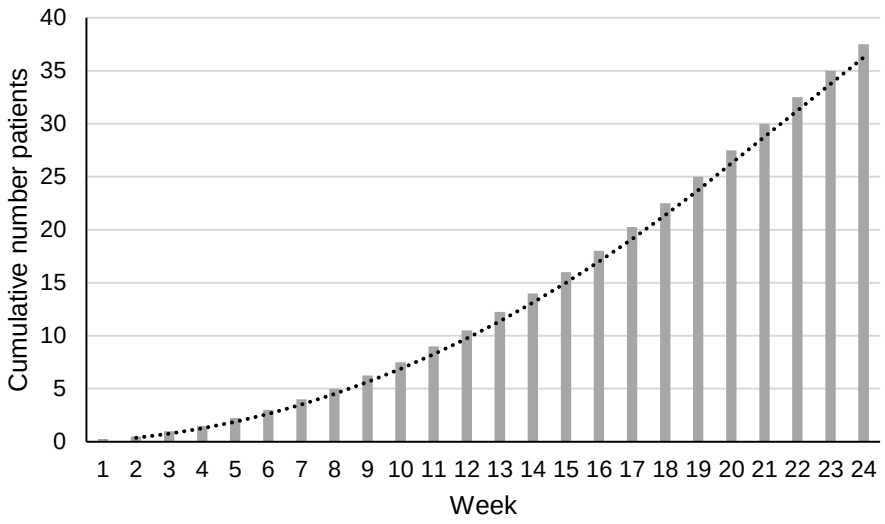
2. Both parts: Objective response rate (best response) of induction treatment (ORR1), objective response rate (best repsonse) of maintenance treatment (ORR2), duration of response (DOR1 and DOR2) and disease control rate (DCR1 and DCR2) according to investigators assessed RECIST v1.1 and OS

3. Both parts: Frequency, grading and severity of AEs, frequency of dose interruptions and reductions

4. Both parts: ORR1 and ORR2, DOR and DOR2, DCR1 and DCR2 according to investigators assessed RECIST v1.1 and OS in pre-specified patient subgroups</td></tr>
<tr><td>3.5 Exploratory objectives</td><td>1. Both parts: To analyse pre-treatment samples for multiple cancer related genes in order to assess potential predictive markers for response and resistance

2. Both parts: To determine mechanisms of primary and acquired resistance to osimertinib monotherapy and the trial treatment in ctDNA and tissue</td></tr>
</table>

	samples collected at progression 3. Both parts: To assess the value of ctDNA for the monitoring of treatment efficacy and treatment guidance *For a detailed description of the exploratory and translational analyses, please, see Attachments.*
3.6 Exploratory endpoints	1+2. Both parts: Targeted next-generation DNA and RNA sequencing (NGS), FISH, phospho-immunoblots of pre-treatment tumor samples and progression tumor samples, and 3' RNA sequencing if feasible 3. Both parts: NGS of ctDNA at baseline, during treatment and at progression *For a detailed description of the exploratory and translational analyses, please see Attachments.*
3.7 Patient number calculations and statistics	*3.7.1. Safety run-in part:* The primary objective of the safety run-in part is the determination of the RP2D of the maintenance treatment (amivantamab, lazertinib and bevacizumab) based on the evaluation of DLTs during the first two cycles of the maintenance part (first 21 days). Starting with the high dose (dose level 1) at most 6 patients will be treated. If a DLT is observed in two patients or more, the next cohort of patients will be enrolled at dose level -1. In total a maximum number of 12 patients will be recruited in the safety run-in part. The doses of the respective drugs will be adapted to the nature of the DLT observed (e.g. EGFR inhibitor-related DLTs occur, then the lazertinib dose will be reduced). For this, specific DLT criteria will be defined. *3.7.2. Main trial part:* The patient number enrolled in the main trial part is calculated in order to estimate the primary endpoint of PFS. The calculation is based on the following assumptions: H0 (mPFS) = 8 months (estimate for current chemotherapy regimens) H1 (mPFS) = 14 months (estimate for new regimen) Power = 0.8 Alpha = 0.05 One-sided test N = 50 To account for 10% drop-out, up to 55 patients will be enrolled. Patients treated within the safety run-in phase at the RP2D will be eligible for end point analysis and count into the total patient number. **N_{total} = 55 patients**

3.8 Predicted enrolment	 *Figure 3. Predicted enrolment for the main trial part (n=43), anticipating the recruitment of one patient per site and month* Approximately 24 weeks (6 months) of enrolment (FPFV to LPFV) are predicted for the main trial part, assuming that 12 patients were enrolled in the safety run-in part. Accounting for interruptions and delays, a total enrolment period of 8 months is anticipated. Enrolment in the safety run-in part follows a de-escalating 3+3 design. The DLT period comprises the first 4 weeks of the maintenance period. In total, an enrolment and DLT observation period of 8 weeks is anticipated for each 3-patient cohort. Thus, approximately 32 weeks (8 months) of enrolment are predicted for the safety run-in part. Total anticipated enrolment period = 16 months
4. Organizational structure and cooperating institutions	
4.1 Sponsor	University of Cologne, Albertus-Magnus-Platz, 50923 Cologne, Germany Represented by: Lung Cancer Group Cologne
4.2 Principal investigator	Sebastian Michels, MD
4.3 Project management	Lung Cancer Group Cologne, University Hospital Cologne, Cologne
4.4 Safety management	TBD
4.5 Responsible statistics institute	Institute of Medical Statistics and Computational Biology, University of Cologne, Cologne
4.6 Cooperation partners for molecular analyses	TBD

4.7 Cooperation partners for translational endpoints	Institute of Pathology, University Hospital Cologne, Cologne (Prof. Reinhard Büttner and Prof. Axel Hillmer)

5. Provisional key eligibility criteria	
5.1 Key inclusion criteria	1. Written informed consent must have been obtained prior to any screening procedures. 2. Patients (male or female) ≥ 18 years of age. Histologically documented, locally advanced or recurrent (stage IIIB who are not eligible for combined modality treatment) or metastatic (stage IV) non-small cell lung cancer harbouring activating *EGFR* mutations as assessed by local testing. 3. Progression while on continuous treatment with osimertinib in the first line or adjuvant setting. No other treatment may have been applied in between osimertinib and the trial treatment. 4. Presence of at least one measurable lesion according to RECIST v.1.1. 5. ECOG performance status ≤2
5.2 Key exclusion criteria	1. Patients with CNS metastases that require increasing doses of steroids or local ablative therapy 2. Patients with carcinomatous meningitis 3. Any acute or chronic medical, mental or psychological condition, which in the opinion of the investigator would not permit the patient to participate or complete the study or understand the patient information 4. Known HIV infection or history of HIV infection independent from the cellular immune status 5. Presence or history of any other primary malignancy other than NSCLC within 5 years prior to enrolment into the trial. Except from this: Adequately treated basal or squamous cell carcinoma of the skin or any adequately treated in situ carcinoma 6. Unable or unwilling to swallow tablets or capsules 7. Patients with impaired gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of EGF816 (e.g. ulcerative diseases, uncontrolled nausea, vomiting diarrhoea, or malabsorption syndromes) 8. Laboratory values as listed below, that cannot be corrected to normal limits within screening: a. TBD 9. Patients receiving treatment with any medication that are known to be a. TBD 10. Patients with a history of or presence of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis 11. Pregnancy or breastfeeding/nursing women 12. Women of child-bearing potential unless they use highly effective methods of contraception during treatment and for four months after withdrawal of study treatment 13. Sexually active males unless they use a condom during intercourse for the time of study treatment and for four months after the withdrawal of study treatment

6. Time lines and preliminary cost calculation	
6.1 Trial duration / timelines	Inclusion first patient (FPFV): 6 months from contract finalization (estimate Q4 2021) Inclusion last patient: FPFV + 16 months Last patient last visit (LPLV): FPFV + 36 months
6.2 Cost calculation	See Appendix

2. References

Ahn MJ, et al. Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1–2 study. Lancet Oncol 2019;20(12):1681-1690.

Blakely CM, et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. Nat Genet 2017;49(12):1693-1704.

Cho BC, et al. Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd-generation tyrosine kinase inhibitor (TKI), in advanced EGFR NSCLC. Ann Oncol 2020;31:S813.

CLCGP and NGM. A genomics-based classification of human lung tumors. Sci Transl Med 2013;5(209):209ra153.

Haura EB, et al. JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2019:37(15_suppl):9009-9009

Hosomi Y, et al. Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study. J Clin Oncol 2020;38(2):115-123.

Michels S, et al. Genomic Profiling Identifies Outcome-Relevant Mechanisms of Innate and Acquired Resistance to Third-Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy in Lung Cancer. JCO Precis Oncol 2019;3:PO.18.00210.

Mok TS, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376(7):629-640.

Nakagawa K, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20(12):1655-1669.

Noronha V, et al. Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in EGFR-Mutated Lung Cancer. J Clin Oncol 2020;38(2):124-136.

Oxnard G, et al. Assessment of Resistance Mechanisms and Clinical Implications in Patients With EGFR T790M-Positive Lung Cancer and Acquired Resistance to Osimertinib. JAMA Oncol 2018;4(11):1527-1534.

Park K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016;17(5):577-789.

Piotrowska Z, et al. Landscape of Acquired Resistance to Osimertinib in EGFR-Mutant NSCLC and Clinical Validation of Combined EGFR and RET Inhibition with Osimertinib and BLU-667 for Acquired RET Fusion. Cancer Discov 2018;8(12):1529-1539.

Ramalingam SS, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382(1):41-50.

Reck M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med 2019;7(5):387-401.

Nakagawa K, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Dec;20(12):1655-1669.

Rosell R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13(3):239-246.

Saito H, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol 2019;20(5):625-635.

Schiller JH, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346(2):92-98.

Sequist LV, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011;3(75):75ra26.

Sequist LV, et al. Osimertinib plus savolitinib in patients with EGFR mutation-positive, MET-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study. Lancet Oncol 2020;21(3):373-386

The Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543–550.

Wu YL, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18(11):1454-1466.