Synopsis

<table>
<tr><td>Title</td><td>Osimertinib plus chemotherapy as 1st-line therapy in stage IV NSCLC patients with atypical EGFR mutations</td></tr>
<tr><td>Short title</td><td>FLAURARE</td></tr>
<tr><td>Trial type</td><td>Single-arm, open-label, phase II</td></tr>
<tr><td>Objectives / endpoints</td><td>Primary objective:
To evaluate the efficacy of osimertinib along with chemotherapy in stage IV NSCLC patients with atypical EGFR mutations (EGFR mutations in Exons 18-21 excluding L858R, Exon 19 del, Exon 20 Ins or T790M mutation).
<u>Corresponding endpoint:</u>
• Progression-free survival rate at 12 months (PFS@12) according to RECIST 1.1, defined as the proportion of patients alive with non-progressive disease 12 months after enrollment and estimated by the Kaplan-Meier method.

Secondary objectives:
To evaluate the efficacy as well as to assess the safety and impact on the quality of life of the patients of osimertinib along with chemotherapy in stage IV NSCLC patients with atypical EGFR mutations (EGFR mutations in Exons 18-21 excluding L858R, Exon 19 del, Exon 20 Ins or T790M mutation).
<u>Corresponding endpoints:</u>
• PFS
• Overall survival (OS)
• Objective response rate (ORR) according to RECIST 1.1
• Toxicity according to CTCAE v5.0
• Quality of life (QoL) as assessed with the QoL questionnaires EQ-5D-5L
• PFS2 as defined by time from initial trial randomization to second disease progression or death from any cause

Exploratory objective:
To identify predictors for clinical outcome.
<u>Corresponding endpoints</u>
• Analysis of ctDNA clearance during treatment
• Identification of mechanisms of resistance</td></tr>
<tr><td>Trial design</td><td>The trial will evaluate the combinational use of pemetrexed based chemotherapy plus the EGFR tyrosine kinase inhibitor osimertinib in patients with stage IV NSCLC with atypical EGFR mutations (EGFR mutations in Exons 18-21 excluding L858R, Exon 19 del, Exon 20 Ins or T790M mutation).
All patients eligible will receive:
• Osimertinib 80 mg QD
PLUS
• Chemotherapy</td></tr>
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	• 4 cycles: Carboplatin AUC5 or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 (Q3W) • Followed by maintenance therapy with pemetrexed (500 mg/m^2, Q3W) for up to 24 months OR until RECIST-defined disease progression, unacceptable toxicity or patient's request or investigator's decision, whatever occurs first. Overall, patients will be followed up for up to 25 months after last patient in (max. treatment duration plus safety follow up 30 days after last treatment) or until death, withdrawal of consent, or loss to follow-up (whichever occurs first).
Rationale	The prevalence of atypical EGFR mutations (mutations in Exons 18-21 excluding L858R, Exon 19 del, Exon 20 Ins or T790M mutation) is up to 30% of all EGFR mutations, occurring in 10-15% of lung adenocarcinoma cases [Robichaux et al. 2021]. The subgroup of patients with atypical EGFR mutations other than exon 20 insertions comprises approximately 2-3% of all NSCLC cases and thus represents a substantial patient population. Recent investigations on the outcome of patients with atypical EGFR mutations in the National Network Genomic Medicine (nNGM) in Germany indicates that, with the exception of most exon 20 insertion mutations, these patients benefit from EGFR TKI treatment, even the subgroup of patients with ultrarare EGFR mutations [Janning et al. 2022]. These data are in line with previously published data mostly containing more common atypical EGFR mutations such as G719X, L861Q and S768I [Robichaux et al. 2021; Yang et al. 2015; Cho et al. 2020, Yang et al. 2022]. However, it is currently still unclear and subject of ongoing work whether patients with specific mutations respond better or worse to different EGFR TKI. First results indicate a lower efficacy of EGFR TKI in patients with atypical EGFR mutations. Thus, overall PFS was 8.2 months for patients with atypical EGFR mutations under monotherapy with the TKI osimertinib [Cho et al. 2020], which is shorter compared to the median PFS of 18.9 months observed in patients with classical EGFR mutations [Soria et al. 2018]. Therefore, identification of a more effective treatment regimen in patients with atypical EGFR mutations is warranted. Since real-world data indicated that the combination of first-generation EGFR TKIs with chemotherapy has a promising benefit on the PFS of NSCLC patients with uncommon EGFR alterations [Xu et al. 2021], this combination appears to be a promising strategy. Based on these data, we hypothesize that the combination of the third generation TKI with pemetrexed-based chemotherapy increase the anti-tumor activity in patients with advanced NSCLC with atypical EGFR mutations in the first-line setting. Therefore, the phase II FLAURARE trial will evaluate the efficacy of osimertinib in combination with pemetrexed-based chemotherapy in untreated patients with stage IV NSCLC harboring EGFR mutations other than

	exon 21 L858R substitution, exon 19 deletions, exon 20 insertion or exon 20 T790M substitution.
Inclusion criteria	1. Patient* has provided written informed consent 2. Patient 18 years or older at time of signing the informed consent form 3. Patient has histologically or cytologically confirmed stage IV NSCLC (adenocarcinoma) 4. Patient did not receive prior systemic treatment for metastatic stage 5. Patient has one or more EGFR mutations in Exons 18-21 excluding L858R, Exon 19 del, Exon 20 Ins or T790M mutation (tested locally) 6. Patient has negative molecular testing for ALK and ROS1 alterations (tested locally) 7. Patient has ECOG performance status ≤ 1 8. Patient must have a life expectancy ≥ 12 weeks 9. Patient has at least one measurable lesion according to RECIST v1.1 10. Patient has adequate hepatic, renal and bone marrow function k. Hemoglobin ≥ 9.0 g/dL l. Absolute neutrophil count ≥ 1.5 x 10^9 /L m. Platelets ≥ 100 x 10^9 /L n. Calculated creatinine clearance ≥ 60 mL/min (use of CKD-EPI formulation is highly recommended) and creatinin ≤ 1.5x upper limit of normal (ULN) o. Serum bilirubin ≤ 1.5 x ULN (or ≤ 3 x ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinemia] or liver metastases) p. AST/ ALT and alkaline phosphatase ≤ 2.5 x ULN (or ≤5 times ULN in the presence of liver metastases) q. International normalized ratio (INR)/ Activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants 18. Female patients who are considered as woman of childbearing potential (WOCBP) must agree to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period as well as up to 2 months after last dose of

	osimertinib or up to 6 months after last dose of chemotherapy, whatever is later. 19. WOCBP must have a negative serum pregnancy test and not be breast-feeding prior to start of the trial treatment 20. Male patients with WOCBP partners must agree to remain abstinent (refrain from heterosexual intercourse) or use barrier contraceptive during the treatment period as well as up to 4 months after the last dose of osimertinib 3 months after last dose of pemetrexed or up to 6 months after last dose of carboplatin or cisplatin , whatever is later. Male patients with a pregnant partner must agree to remain abstinent or to use a condom for the duration of the pregnancy. * Patients are included regardless of their gender.
Exclusion criteria	1. Mixed histology (small-cell and non-small cell or non-squamous and squamous; patients exhibiting the latter expression pattern may be eligible if the adenocarcinoma part predominates in >50% of analyzed tumor tissue) 2. Patients having received any prior therapy with an EGFR TKI 3. Patient is candidate for complete removal of oligometastatic disease. If patients refuse to undergo surgery/ablations they are allowed into the trial 4. Patient received treatment with an investigational drug within five half-lives of the compound or 3 months before start of the trial treatment, whichever is greater 5. Patient is currently receiving (or unable to stop prior start of the trial treatment) medications or herbal supplements known to be strong inducers of CYP3A4 (at least 3 weeks prior) (see Appendix 3). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4 6. Patient has symptomatic, neurologically unstable CNS metastases or requiring increasing doses of steroids to manage CNS symptoms within 2 weeks prior to trial entry (maximal acceptable dose must be ≤ 10 mg of prednisolone) 7. Patient has any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of start of trial treatment, with exception of alopecia and grade 2 prior platinum-therapy-related neuropathy 8. Patient has any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator’s opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol 9. Patient has known active infection (e.g., patients receiving treatment for infection) including hepatitis C and human

	immunodeficiency virus (HCV/ HIV), or active uncontrolled HBV infection. Screening for chronic conditions is not required. Patients with chronic/ resolved HBV are eligible if they meet the following criteria: • Negative for hepatitis B surface antibody (HBsAb) and positive for hepatitis B core antibody (HBcAb). In addition, patients must be receiving anti-viral prophylaxis for 2- 4 weeks prior to study treatment OR • Positive for HBsAg, but for > 6 months have had transaminases levels below ULN and HBV DNA levels below <100 IU/mL (i.e., are in an inactive carrier state). In addition, patients must be receiving anti-viral prophylaxis for 2-4 weeks prior to study treatment *NOTE: Following assessments are recommended for patients with resolved or chronic (inactive carrier state) or active controlled HBV infection while on treatment with osimertinib* a. monthly *monitoring of ALT/AST, HBV DNA levels and HBsAg (if negative at baseline)* b. *where liver signs and symptoms of viral reactivation appear (HBV DNA levels exceeding 10-fold from baseline or ≥100 IU/mL (if baseline HBV DNA levels are undetectable) or conversion of HBsAg negative to positive) consult an expert hepatologist/specialist and consider interruption or discontinuation of study treatment, based on risk-benefit assessment* 3. Patient has refractory nausea and vomiting, chronic gastrointestinal disease, inability to swallow tablets or previous significant bowel resection that would preclude adequate absorption of osimertinib 4. Patient has any of the following cardiac criteria: • Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value • Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block and second degree heart block • Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: Serum/plasma potassium < LLN; Serum/plasma magnesium < LLN; Serum/plasma calcium < LLN) , congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes (see Appendix 4) 12. Leptomeningeal disease

13. Patient has past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease
14. Known additional malignancies other than NSCLC, either untreated or having required active treatment within the past 3 years
15. Known allergy or hypersensitivity to any component of the chemotherapy regimen or to osimertinib or any constituents of the products
16. Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the patient's participation in the trial.
17. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.

Sample size

Based on feasibility, the required sample size is 40.

The FLAURA2 trial demonstrated a median PFS of 16.7 months for patients treated with osimertinib monotherapy and of 25.5 months for patients treated with osimertinib in combination with pemetrexed-based chemotherapy [Planchard et al. 2023]. In addition, osimertinib monotherapy in patients with uncommon EGFR mutations resulted in a media PFS of 8.2 months in the KCSG-LU15-09 trial [Cho et al. 2019]. Based on the given data, we expect a median PFS of about 18 months in the present FLAURARE trial.

The following table shows results from simulating survival data of 40 patients based on the Weibull distribution using SAS v9.4, for various censoring rates and median PFS times around 18 months:

mPFS	Censoring Rate	PFS@12 [95%-CI]	Halfwidth of 95%-CI
17.37	40.0%	0.68 [0.52, 0.84]	0.16
17.59	40.0%	0.66 [0.49, 0.82]	0.165
18.01	40.0%	0.59 [0.43, 0.75]	0.16
18.71	45.0%	0.69 [0.53, 0.84]	0.155
18.87	45.0%	0.71 [0.56, 0.85]	0.145
18.17	50.0%	0.62 [0.45, 0.80]	0.175
18.52	50.0%	0.61 [0.44, 0.78]	0.17
17.97	50.0%	0.73 [0.57, 0.88]	0.155
18.79	52.5%	0.73 [0.59, 0.88]	0.145
19.35	52.5%	0.76 [0.62, 0.91]	0.145
18.99	55.0%	0.69 [0.53, 0.85]	0.16
17.98	55.0%	0.70 [0.54, 0.85]	0.155
18.99	55.0%	0.69 [0.53, 0.85]	0.16
17.11	57.5%	0.66 [0.49, 0.84]	0.175
17.08	60.0%	0.61 [0.42, 0.80]	0.19
18.54	62.5%	0.53 [0.35, 0.72]	0.185
18.68	67.5%	0.71 [0.53, 0.89]	0.18

	The halfwidth of the 95% confidence intervals ranges between 0.145 and 0.19, which is considered sufficiently precise to generate a signal and pursue the concept of a large trial.
Efficacy evaluations/ criteria	On treatment, imaging assessments will be performed at baseline, 6 weeks (Q6W ± 7 days), 12 weeks (Q12W ± 7 days) after enrollment and then Q12W (± 7 days) during treatment and responses will be assessed using RECIST 1.1. Subjects who discontinue trial intervention for reasons other than disease progression will have post-treatment follow-up for disease status. Imaging assessments performed independently of the study participation should be documented (Q24W ± 14 days recommended) until progression, initiation of another anti-cancer treatment, withdrawing consent, lost to follow-up, death or end of the trial, whichever occurs first. All subjects will be followed for OS for maximum of 25 months after last patient in, until death, withdrawing consent or loss to follow-up, whichever occurs first.
Safety evaluation	Adverse events (AE) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. All (serious) AEs will be monitored starting from first administration of trial treatment until 30 days after the last dose or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events (SAEs) that are believed to be related to prior treatment with trial drug or study procedures. After informed consent has been obtained but prior to initiation of the trial treatment, only SAEs caused by a protocol-mandated intervention should be reported.
Collection of biosamples for translational research	This clinical trial will be accompanied by a comprehensive translational research program (might be modified or expanded taking latest scientific data into account). Archival tumor tissue and re-biopsy material at time of disease recurrence, both collected as per local standard of care, as well as blood samples at screening, at day 1 of the second cycle (21 ± 3 days after treatment initiation) and at time of disease progression will be collected for future biomarker analysis in separate translational research (TR) project.
Statistical analysis	The primary endpoint PFS rate at 12 months estimated by the Kaplan-Meier method together with its 95% confidence interval (CI) will be provided. Categorical variables will be summarized by frequency distributions (number, percentages of subjects, and missing values); continuous variables will be summarized by number of subjects (N), mean, standard deviation, median, first and third quartile, minimum, maximum, missing values. Time-to-event endpoints will be summarized using Kaplan-Meier methods and displayed both graphically and in tabular form. The tables contain the number of events, median and 25% and 75% percentile of the survival, and the survival rates at certain times with confidence intervals. Statistical analysis for the secondary, exploratory and safety endpoints will also be primarily descriptive in nature.

	Safety: Frequency tables will be compiled with the number and percentage of patients experienced the AE by treatment and total. Additionally, AEs will be summarized by seriousness of AE, relationship to the trial drug, and grading for all NCI CTC categories. QoL will be summarized using descriptive statistics and change in EQ-5D-5L before and after treatment at respective time points by treatment and total.
Number of trial sites	approximately 20
Duration of the trial (planned)	The estimated trial duration of the trial is 49 months (18 months recruitment plus 25 months follow up after last patient in, added to 6 months of set up as well as cleaning and other closing activities). The global end of this trial is defined as the date of database closure to ensure the collection of survival data of patients and the active involvement of sites in the data cleaning process (e.g., addition source data may be requested or an additional monitoring visit may be necessary). The Sponsor may decide to terminate the trial at any time (refer to protocol section 5.6.2 for criteria for early trial termination).