AIO-YMO/TRK-0120: Radiation during Osimertinib Treatment: a Safety and Efficacy Cohort Study (ROSE)

AIO-Studie

Studiennummer/-Code:	**AIO-YMO/TRK-0120 / ROSE**
Status:	in Rekrutierung
Rekrutierungszeit:	von: Q1/2022 bis: Q3/2024
Anzahl Zentren:	geplant: 8-10 aktuell initiiert: 8 aktiv rekrutierend: 1
Weitere Zentren:	erwünscht
Anzahl Patienten:	geplant: 60 aktuell eingeschlossen: 6
Letzte Aktualisierung	Oktober 2022

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CONDITION	EGFR-mutation positive NSCLC, treatment with osimertinib
DESIGN	Single arm, explorative, multi-center parallel cohort study
Primary objective	To assess the safety of osimertinib treatment continuation during irradiation therapy for palliation or oligoprogressive disease.
Secondary objectives	To assess the efficacy of osimertinib treatment continuation during irradiation therapy for palliation or oligoprogressive disease.
Exploratory objectives	To investigate types of irradiation (conventional vs. stereotactic) and target volumes used. To explore blood- and tissue-based biomarkers in this setting
Primary endpoint	• Safety and tolerability (Frequency, time of onset and severity of Adverse Events, grading according to CTCAE V5.0), including pneumonitis, interstitial lung disease, radiation pneumonitis, radionecrosis and cardiac failure (congestive heart failure – CHF) as adverse events of special interest. • Pneumonitis. A consensus definition of pneumonitis based on symptoms, clinical examination, imaging and pulmonary function testing, as well as any available bronchoscopy results, will be used. In the absence of bronchoscopy, pharyngeal wash should be used to exclude viral infections. Care should be taken to differentiate between drug-induced and radiation-induced pneumonitis, by taking into account the localization (in-field or outside irradiated area) and time of onset relative to treatment. Pneumonitis severity is defined according to CTCAE V5.0:

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self care ADL; oxygen indicated

	<table><tr><td>Grade 4</td><td>Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)</td></tr><tr><td>Grade 5</td><td>Death</td></tr></table> • Radionecrosis: A consensus definition of radionecrosis based on imaging and clinical consultation will be used.
Secondary endpoints	• Progression-free survival (PFS), calculated as PFS1, PFS2, PFS3, PFS0 to assess osimertinib treatment continued beyond several progression events entailing radiotherapy, and prior to first radiotherapy • Time to treatment failure (TTF) • Local tumor control • Overall survival (OS) • Quality of Life assessed by EORTC QLQ-C30
INTERVENTION(S)	Osimertinib: according to its marketing authorization, i.e. at daily doses of 80 mg, for a maximum of 12 months within the study. Radiotherapy: according to standard of care.
Exploratory analysis / translational research endpoints	• Blood sample analysis and biomarker assessment • Optional tumor tissue analysis (pre-study FFPE sample) and biomarker correlation with patient baseline characteristics and outcomes • Target volume of irradiation • Type of irradiation (conventional, stereotactic)
BACKROUND/RATIONALE	Many patients with advanced lung cancer require palliative irradiation of metastases to relieve symptoms and prevent local complications. In addition, guidelines recommend local treatment (including radiation) for oligoprogression during TKI treatment. Clinicians are faced with the decision whether to continue TKI therapy during irradiation, a practice for which there is little data, or to interrupt the oral treatment for the duration of radiation, which may lead to progression of non-irradiated lesions. For erlotinib and gefitinib there is some data indicating that cranial irradiation as well as stereotactic body irradiation may be carried out safely without discontinuing or interrupting the TKI treatment. There is very limited data on the safety of osimertinib during irradiation, and no evidence-based recommendations around stopping osimertinib for irradiation.
Inclusion criteria	1. Provision of written informed consent prior to any study specific procedures, including screening evaluations that are not SOC. 2. Age ≥ 18 years at time of study entry. 3. Histologically confirmed NSCLC 4. Ongoing or planned osimertinib treatment according to marketing authorization (first line treatment of tumor positive for an activating EGFR mutation, or later line treatment of tumor positive for EGFR T790M mutation, assessed according to local standard. First line therapy is defined as therapy used to treat advanced disease. Each subsequent line of therapy is preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy. Experimental therapies when given as separate regimen are considered as separate line of therapy. Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.) 5. Clinical indication for palliative radiotherapy of one or more lesions, either for local symptom control of primary tumor or metastasis, or for oligoprogressive metastasis, with conventional or stereotactic strategy. Radiotherapy of metastatic sites can be for bone, solid organ or soft-tissue lesions; initial size of brain metastases should be < 3 cm. Lung lesions should be no more than 5 cm. 6. ECOG performance status 0-2. 7. Life expectancy ≥12 weeks 8. Female subjects should be using highly effective contraceptive measures, and must have a negative pregnancy test and not be breast-feeding prior to start of dosing if of child-bearing potential or must have evidence of

	non-child-bearing potential by fulfilling one of the following criteria at screening: • Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments • Women under 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution. • Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation • Further information in Section 7.1.1 and Appendix 21.7 9. Male subjects who are sexually active with WOCBP should be willing to use highly effective contraception (see Section 7.1.1 and Appendix 21.7). Men who are azoospermic do not require contraception. 10. The patient is willing and able to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations. 11. Negative COVID-19 test within 1 week prior to starting irradiation if clinically required by current regional COVID-19 outbreak situation.
Exclusion criteria	1. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study, or during the follow-up period of an interventional study. 2. Treatment with an investigational drug within five half-lives of the compound or 3 months, whichever is greater 3. Previous enrolment in the present study. 4. Any chemotherapy, biologic or hormonal cancer therapy other than EGFR-TKIs used concurrently or within 4 weeks prior to study enrolment, or checkpoint inhibitors within 130 days prior to study enrolment. Hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable. 5. Any unresolved toxicities from prior therapy greater than grade I (exception: alopecia, grade 2 neuropathy) which in the investigator's opinion would jeopardise compliance with the protocol or worsen during irradiation 6. Cardiac side-effects of osimertinib not sufficiently improved by dose reduction as suggested by the label/ German "Fachinformation". 7. In patients with indication for radiotherapy of lung lesions: past medical history of ILD/pneumonitis, radiation pneumonitis grade 2 or greater (CTCAE V5.0) or requiring steroid treatment, or any evidence of clinically active ILD, in particular interstitial pulmonary fibrosis (IPF). 8. Major surgery (as defined by the Investigator) within 4 weeks prior to starting the study; patients must have recovered from effects of preceding major surgery. Note: Local non-major surgery for palliative intent (e.g., surgery of isolated lesions) is acceptable. 9. Congenital long QT syndrome 10. 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. • Patient with 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 11. Inadequate bone marrow reserve or organ function (as demonstrated by any of the following laboratory values: • Absolute neutrophil count <1.5 x 10^9/L; • Platelet count <100 x 10^9/L; • Hemoglobin <90 g/L (9 g/dL); • Alanine aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; • Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; • Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinemia] or liver metastases; • Serum creatinine >1.5 times ULN concurrent with creatinine clearance <50 mL/min [measured or calculated by Cockcroft and Gault equation]—confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN. 12. 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 jeopardise compliance with the protocol, or active infection. Screening for chronic conditions is not required, inclusion of controlled chronic infections (e.g. HIV) is permitted. Participants with a resolved or chronic infection HBV are eligible at discretion of the treating physician. 13. 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. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib. 15. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements. 16. Active infection will include any patients receiving treatment for infection. 17. Clinical suspicion of COVID-19 with or without negative COVID-19 test 18. Participants with a resolved or chronic HBV infection are eligible if they are: • Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG] or • Positive for HBsAg, negative for HBeAg but for > 6 months have had transaminases levels below ULN and HBV DNA levels below 2000 IU/mL (i.e., are in an inactive carrier state). 19. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib. 20. Currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of CYP3A4 (at least 3 week prior) (Section 21.5). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4. 21. Women who are pregnant or breast-feeding 22. Male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 4 months after the last dose of Osimertinib 23. 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]

TRIAL DURATION	Enrollment: 24 months Total study duration: ~48 months
Sample size estimation	The study objective is exploratory in nature. Therefore, no formal hypothesis test is formulated. Instead, the sample size will be gauged against the objective to observe/acquire meaningful data about the potential toxicities. In this regard, the sample size of N=60 is considered to provide a reasonably reliable estimate. With a sample size of N=60 -assuming that the number of events follows a binomial distribution [B(60,p)]-, events with an incidence rate p > 4,9% will be observed at least once with a 95% probability. Assuming 30% grade 3/4 all-cause AEs during osimertinib* monotherapy, a clinically significant increase in AEs (defined as 48% grade 3 or higher AEs) with simultaneous radiation at any point during osimertinib treatment, will be well within the detection limit of the ROSE trial.
PARTICIPATING CENTERS	8-10
FURTHER CENTERS DESIRED?	yes
NUMBER of PATIENTS	60 (at least 10 per cohort)