A PHASE I-III, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE THERAPIES IN COHORTS OF PATIENTS SELECTED ACCORDING TO BIOMARKER STATUS, WITH LOCALLY ADVANCED, UNRESECTABLE, STAGE III NON-SMALL CELL LUNG CANCER

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This study has been transitioned to CTIS with ID 2023-503920-14-00 check the CTIS register for the current data. The overall objectives of this study are to evaluate the efficacy and safety of multiple therapies in patients with locally advanced,...

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53740

Source
ToetsingOnline

Brief title
not available

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
NSCLC non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Chugai Pharmateutical Ltd,Roche

Intervention

Keyword: lung cancer, non-small cell lung cancer, NSCLC, stage III

Outcome measures

Primary outcome

For all cohorts, the primary efficacy endpoint is blinded independent central review (BICR)-assessed progression-free survival (PFS), as defined as the time from the randomization (or from first IMP intake) to the first documented disease progression according to RECIST v1.1 or death from any cause, whichever occurs first.

The difference between the treatment arms will be assessed and tested for the following hypothesis: the survival distribution function of the treatment arm is the same as for the durvalumab treatment arm versus the alternative that the two distributions are different.

See protocol page 95, cohort A1 page 196, 200-201

Secondary outcome

Secondary endpoints:

- Time to CNS progression (blinded independent central review and Investigator,

per RECIST)

- distant metastasis-free survival (blinded independent central review)

- Progression Free Survival (Investigator per RECIST)

- objective response rate, duration of response (blinded independent central

review and Investigator, per RECIST)

- Overall Survival (descriptive)

- Safety

- Time to confirmed deterioration of the disease

See protocol cohort A1 page 196, 200-201

Study description

Background summary

Assigning treatments that specifically target actionable oncogenic drivers is the cornerstone of precision oncology. Oncogenic driver alterations play a critical role in cancer development and maintenance, and this is what distinguishes them from passenger mutations.

Progress in the identification of oncogenic mutations and chromosomal rearrangements has provided new opportunities to develop targeted therapeutic agents for the treatment of advanced and metastatic NSCLC. Receptor tyrosine kinases (RTKs) are key regulatory signaling proteins governing cancer cell growth and metastasis. During the last two decades, several tyrosine kinase inhibitors targeting RTKs have been designed to target the aberrant downstream activity of oncodriver alterations. Such molecules have favorable benefit-risk profiles compared with that of traditional cytotoxic chemotherapy. Assigning rational treatments based on the presence (or absence) of predictive oncology biomarkers is now a cornerstone in the clinical management of patients with advanced or metastatic NSCLC. Multiple targeted therapies have been approved globally for metastatic disease, including alectinib for ALK-positive NSCLC, entrectinib for ROS1-positive NSCLC, and pralsetinib for RET fusion positive NSCLC.

As a result of the availability of approved targeted therapies, the NCCN recommends broad molecular profiling in patients with metastatic NSCLC. Similarly, the ESMO guidelines also recommend molecular testing to identify specific therapy response-predictive biomarkers in advanced NSCLC.
As treatment options advance for early stage to locally advanced NSCLC, it is envisaged that in the future, molecular testing will not be limited only to patients with advanced or metastatic disease, and will expand to address earlier stages of NSCLC.

The use of platform trials has emerged as efficient means of evaluating multiple treatment regimens in multiple biomarker-defined patient populations within the same trial infrastructure. This approach has enabled greater patient access to the most appropriate investigational therapies based on the patient*s biomarker status. Platform trials allow for the addition of new cohorts via protocol amendments or closure of individual cohorts whilst the study is ongoing. These trials may be amended as new potential therapies emerge for investigation in selected patients. As mentioned, multiple targeted therapies have already been approved globally in advanced or metastatic NSCLC, and this platform study will enable their evaluation in the treatment of Stage III unresectable disease, for which a medical need remains unmet despite recent advances in its treatment.

Recent approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency of durvalumab consolidation therapy after two cycles of platinum-based (concurrent) CRT in patients with locally advanced, unresectable, Stage III NSCLC validates the inhibition of the PD-L1 pathway for achieving clinical benefit.

In light of this validation, evaluating targeted therapies in Stage III, unresectable NSCLC is appropriate in patients with oncogenic alterations because this approach has proven to be highly effective in treating advanced or metastatic disease and when used as adjuvant therapy.

See protocol pages 42-45.

Study objective

This study has been transitioned to CTIS with ID 2023-503920-14-00 check the CTIS register for the current data.

The overall objectives of this study are to evaluate the efficacy and safety of multiple therapies in patients with locally advanced, unresectable, Stage III NSCLC who are selected according to biomarker status as identified by tissue-based testing.

Primary and secondary efficacy objective
To evaluate the efficacy of study treatment (alectinib or entrectinib or

pralsetinib) compared with durvalumab in the study specific patient population.

Additional Secondary efficacy objective
To evaluate the health-related quality of life of the study specific patient population in the study treatment arm compared with in the durvalumab arm.

Exploratory efficacy objective
To evaluate the health-related quality of life of participants treated with study treatment compared with durvalumab in the study specific patient population.

Safety objective
To evaluate the safety and tolerability of study treatment compared with durvalumab in the study specific patient population

Exploratory safety objective
To evaluate the tolerability of study treatment compared with durvalumab in the study specific patient population

Exploratory pharmacokinetic objective
For Cohort A1: To characterize the pharmacokinetics of study drug and its major metabolite

Exploratory biomarker objectives
To assess the predictive and prognostic effect(s) and pharmacodynamics of exploratory biomarkers in tissue and blood, and their association with disease status, mechanisms of resistance, and/or response to study drug

and
To evaluate the efficacy of study drug compared with durvalumab according

Exploratory health status utility objective
To evaluate and compare patients* health status to generate utility scores for use in economic models for
reimbursement

See protocol page 11-14, and section 2, pages 47-48

Study design

Study BO42777 is a Phase I-III, global, multicenter, multicohort study to evaluate the efficacy and safety of multiple therapies in patients with locally advanced, unresectable, Stage III NSCLC with eligible biomarker status. This population is based on the Version 8 of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) NSCLC staging system (Amin et al. 2017).

Patients with tumors harboring a cohort-eligible biomarker identified through one of the methods will be screened for enrollment in the applicable cohort of this study.

This platform treatment study employs a flexible biomarker screening process, wherein biomarker eligibility will be determined through any of the following:
- Central tissue-based biomarker testing at the Sponsor*s designated central laboratory used in Study BX43361 (the Master Screening Study)
- Available results from a Sponsor pre-approved local tissue-based test

With the exception of tissue samples already provided under Study BX43361, all patients screened to Study BO42777 are required to provide pre-cCRT/sCRT tumor tissue and blood for central molecular testing and/or additional study-related biomarker analyses.
Study-eligible patients will be assigned to the appropriate cohort on the basis of their tumor biomarker status and enrolled if they meet the additional cohort-specific eligibility criteria. If more than one cohort-specific biomarker is identified, the priority for cohort assignment will be determined according to the less-prevalent biomarker as follows:
- ROS1 rearrangement (~1%): Cohort A2 (entrectinib)
Mandatory biomarker samples are necessary to evaluate exploratory prognostic and/or predictive biomarkers, including, but not limited to, biomarkers related to driver-oncogene signaling, NSCLC pathogenesis and biological response to study drug.

Treatment, unless otherwise specified, will continue until disease progression (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]), unacceptable toxicity, patient or physician decision to discontinue, maximum duration of study treatment, or death, whichever occurs first. If a patient discontinues treatment
before disease progression (because of an adverse event or other reasons), tumor assessments will continue as specified in the cohort-specific appendix until disease progression, death, withdrawal of consent, or cohort or study closure by the Sponsor, whichever occurs first. Information regarding any blinded independent central review (BICR) will be provided in the cohort-specific appendices of the protocol and BICR charter, as applicable.

After completion or early discontinuation of study drug, whichever occurs first, patients will enter the post-treatment follow-up period of the study. Post-treatment follow-up, including subsequent anti-cancer therapies and survival status assessment, will continue for each patient until death, loss to follow-up, withdrawal of consent from the study, or study or cohort closure, whichever occurs first.

See protocol section 3 pages 48-51.

Intervention

Patients receive oral capsules Alectinib, Entrectinib, and Pralsetinib on daily base or receive the standard of care Durvalumab. The maximum treatment duration for Alectinib, Entrectinib, and Pralsetinib is 3 years and for durvalumab 1 year.

Patients will undergo the following additional interventions:
- tumor assessments at screening, every 8 weeks for the first 48 weeks following treatment initiation, and every 12 weeks thereafter until confirmed investigator-assessed radiographic disease progression per RECIST v1.1, withdrawal of consent, termination of an individual study cohort by the Sponsor, or death, whichever occurs first.
- blood sampling for safety, Biomarkers and PK
- tumor tissue sampling: at screening (if not yet available) and At the time of confirmed radiographic disease progression. Furthermore optional tumor tissue sampling might be done any time prior to confirmed radiographic disease progression for the purpose of disease progression determination (if clinically feasible)

See protocol section 4.5 pages and the cohort specific schedule of activities in appendix 12, 13 and 14.

Study burden and risks

Definitive platinum-based chemotherapy is curative in its intent. Nonetheless, the majority of patients of patients ultimately die of their disease, with recent estimates of 5 year survival in this population, ranging from 13% to 36%. Personalized approaches to the treatment of NSCLC have demonstrated success in the advanced/metastatic setting. Although the clinical efficacy data of tyrosine kinase inhibitors (TKIs) in Stage III NSCLC, is currently limited with clinical trials currently ongoing (such as, osimertinib in EGFRm Stage III NSCLC [NCT03521154]), TKIs have already been demonstrated to provide clinical benefit in other early stage NSCLC settings.

This platform trial design, in conjunction with biomarker screening, provides a means of identifying patients and generating clinical efficacy and safety data to support the selection of treatment for Stage III, unresectable NSCLC. With the careful selection of patients by biomarker status and evaluation of applicable investigational therapies which are expected to provide the most benefit in terms of treatment effect , this is expected to counterbalance any study risks, with a favorable benefit-risk for the study. These innovative means will enable more efficient development of new therapies in biomarker-defined populations, thereby enabling more patients to access beneficial therapeutic options. The study design will provide the investigator with the option to conduct selected study visits

(including safety assessments) utilizing a mobile healthcare professional who will visit the patient at home or another suitable location, as detailed in the cohort specific appendices.
The risks associated with the selected mobile healthcare professional home visits are expected to be similar to those of in clinic visits, whilst reducing the burden on patients of having to travel to clinic for all visits.
The study design includes cohort-specific inclusion and exclusion criteria to ensure patient safety on the basis of the specific risks related the investigational medicinal products (IMPs). The protocol also included applicable safety monitoring and management requirements of the IMPs of interest, including an independent Data
Monitoring Committee (iDMC). These criteria are designed to enhance the safety of patients and enable the assessment of benefit-risk on a cohort basis.

Given the above, the overall benefit-risk profile of the platform study design is positive.

See protocol section 1.4.2 Study Benefit-Risk Assessment page 45-46

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age >=18 years Body weight >=30 kg Whole-body positron emission tomography/computed tomography scan (PET/CT) performed prior and within 42 days of the first dose of cCRT or sCRT Histologically or cytologically documented locally advanced, unresectable Stage III NSCLC of either squamous or non-squamous histology (Version 8, American Joint Committee on Cancer/Union for International Cancer Control NSCLC staging system (Amin et al. 2017). Prior receipt of at least two prior cycles of platinum-based chemotherapy given concurrently with radiotherapy (cCRT); or at least two prior cycles of platinum-based chemotherapy given prior to radiotherapy (sCRT) The RT component in the cCRT or sCRT must have been at a total dose of radiation of 60 (± 10%) Gy (54 Gy to 66 Gy) administered by intensity-modulated radiotherapy (preferred) or three dimension (3D)-conforming technique No disease progression during or following platinum-based cCRT or sCRT Life expectancy >= 12 weeks Documented tumor PD-L1 status Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2 • Adequate hematologic and end-organ function • For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, during the treatment period and for at least 90 days after the final dose of alectinib or durvalumab (Cohort A1 only) Confirmed availability of a representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen Documented ALK fusion positivity (Cohort A1 only)

Exclusion criteria

Any history of previous NSCLC and/or any history of prior treatment for NSCLC Any evidence of Stage IV disease If pleural effusion is present the following criteria must be met to exclude malignant involvement (T4 disease): When pleural fluid is visible on both the computed tomography scan and chest X-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative. Patients with exudative pleural effusions are excluded regardless of cytology. Patients with effusions that are minimal (i.e., not visible on chest X-ray) that are too small to safely tap are eligible NSCLC known to have one or more of the following ALK point mutations, as identified by site local testing or Sponsor central testing: I1171X (where X is any other amino acid), V1180L, G1202R (Cohort A1). NSCLC known to have a known or likely oncogenic-driver mutation in the EGFR gene, as identified by site local testing or Sponsor

central testing Liver disease Positive hepatitis B surface antigen test at screening Patients known to be positive for hepatitis C virus antibody HIV infection, patients are excluded if HIV is not adequately controlled (specific criteria apply). Known active tuberculosis Presence of clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis Grade >= 2 pneumonitis from prior cCRT or sCRT Symptomatic bradycardia (Cohort A1) Any gastrointestinal (GI) disorder that may affect absorption of oral medications Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications Active or history of autoimmune disease or immune deficiency History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on the screening chest CT scan History of malignancy other than NSCLC within 5 years prior to screening Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer Major surgical procedure, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia Treatment with systemic immunostimulatory agents Treatment with live, attenuated vaccine Treatment with investigational therapy within 28 days prior to initiation of study treatment Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment Treatment with systemic immunosuppressive medication Prior treatment with ALK inhibitors. Prior treatment with CD137 agonists or immune checkpoint blockade therapies Prior allogeneic stem cell or solid organ transplantation History of hypersensitivity to alectinib, durvalumab, or any of their excipients. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study Any condition that, in the opinion of the investigator, would interfere with the evaluation of the study drug or interpretation of patient safety or study results Known hereditary problems of galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption Pregnancy or breastfeeding, or intending to become pregnant during the study treatment or within 90 days after the final dose of alectinib or durvalumab (Cohort A1)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-12-2022
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Generic name:	AmoyDx® Pan Lung Cancer PCR Panel and FoundationOne®CDx Assay
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Alecensa
Generic name:	Alectinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Imfinzi
Generic name:	Durvalumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	17-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	01-12-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2023
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-503920-14-00
EudraCT	EUCTR2021-004149-19-NL
ClinicalTrials.gov	NCT05170204
CCMO	NL81382.000.22