A Phase III, Open-label, Randomised, Multicentre Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer Without Actionable Genomic Alterations, and Whose Disease Has Progressed On or After Prior Anti-PD-(L)1 Therapy and Platinum-based Chemotherapy: LATIFY

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This study has been transitioned to CTIS with ID 2023-509429-37-00 check the CTIS register for the current data. In this study, we want to learn more about the effect and safety of Ceralasertib plus Durvalumab on the inhibition of tumour growth, and...

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

Summary

ID

NL-OMON53518

Source
ToetsingOnline

Brief title
LATIFY

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-small Cell Lung Cancer, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Astra Zeneca

Intervention

Keyword: Ceralasertib, NSCLC, Phase III

Outcome measures

Primary outcome

Objective: To demonstrate superiority of ceralasertib plus durvalumab combination therapy relative to docetaxel by assessment of OS in participants with advanced NSCLC after second- or third-line therapy and without actionable genomic alterations.

Secondary outcome

- To demonstrate superiority of ceralasertib plus durvalumab combination therapy relative to docetaxel by assessment of PFS

- To estimate the effectiveness of ceralasertib plus durvalumab*combination therapy relative to*docetaxel by assessment of ORR

- To estimate the effectiveness of ceralasertib plus durvalumab combination therapy relative to*docetaxel by assessment of duration of response (DoR)

- To estimate the effectiveness of ceralasertib plus durvalumab*combination

therapy relative to*docetaxel by assessment of time to response (TTR)

- To estimate the effectiveness of ceralasertib plus durvalumab*combination therapy relative to*docetaxel by assessment of disease control rate (DCR) at 18 weeks

- To estimate the*effectiveness of*ceralasertib plus durvalumab combination therapy*relative to*docetaxel by*assessment of time to second progression or death (PFS2)

- To estimate the effectiveness of ceralasertib plus durvalumab combination therapy relative to docetaxel by assessment of OS at 12 months (OS12)

- To assess participant-reported health-related quality of life (QoL)

- To assess participant-reported physical functioning in participants treated with ceralasertib plus durvalumab combination therapy relative to docetaxel

- To evaluate participant-reported treatment tolerability

- To assess the pharmacokinetic (PK) of ceralasertib when administered in combination with durvalumab

- To assess the safety and tolerability of ceralasertib plus durvalumab combination therapy as compared with docetaxel

Study description

Background summary

Treatment options for patients after progression on platinum-based chemotherapy and PD-(L) containing therapies remain limited. Docetaxel as monotherapy or in combination with nintedanib or ramucirumab is the standard of care, but due its modest efficacy and known treatment-related hematologic toxicity other therapy options are clearly needed for patients who progressed or relapsed after first line combination therapies. Other chemotherapy compounds given as monotherapy

may be other therapy options, but similar to Docetaxel, with modest efficacy. Two ongoing studies show preliminary evidence of efficacy for the combination of Ceralasertib and Durvalumab. Also, Ceralasertib alone, or in combination with Durvalumab, has found to be safe for further investigation in patients with NSCLC, and the combination has the potential to improve outcomes for patients with advanced or metastatic NSCLC.

Study objective

This study has been transitioned to CTIS with ID 2023-509429-37-00 check the CTIS register for the current data.

In this study, we want to learn more about the effect and safety of Ceralasertib plus Durvalumab on the inhibition of tumour growth, and also to better understand NSCLC and associated health problems.
We compare the effect and safety of Ceralasertib plus Durvalumab with the effect of Docetaxel. Docetaxel and Durvalumab are already being used for the treatment of NSCLC.
The combination of Ceralasertib plus Durvalumab is not approved for the treatment of NSCLC.

Study design

This is a Phase III, randomised, open label, two-arm, multicentre, international study assessing the efficacy and safety of ceralasertib and durvalumab combination therapy compared with docetaxel in patients with advanced or metastatic NSCLC that has progressed on prior anti-PD (L)1 therapies and platinum based chemotherapy.

Intervention

Participants will be randomised in a 1:1 ratio to one of the two treatment groups:
• Group A: Ceralasertib plus durvalumab combination therapy
Each 28-day cycle will begin with ceralasertib from Day 1 to Day 7 followed by durvalumab on Day 8 (approximately 290 participants planned)
• Group B: Docetaxel monotherapy
Each 21-day cycle will begin with docetaxel on Day 1 (approximately 290 participants planned)

Participants in Group A will receive ceralasertib oral tablets 240 mg BID for 7 consecutive days (Day 1 to Day 7) and then 1500 mg durvalumab (on Day 8) as an intravenous (IV) infusion every 28 days (q28d).

Participants in Group B will receive docetaxel 75 mg/m2 body surface area (BSA) as IV infusion every 21 days (q21d). Study intervention will continue until

clinical progression, confirmed RECIST 1.1 defined radiological progression, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met. There is no maximum treatment duration defined for either group.

Study burden and risks

- ECG
- blood draw (in total 480-490 mL group A, 270-280 mL group B)
- brain scan every 9 weeks for participants with confirmed brain metastases
- Bone scan every 6 months for participants with confirmed bone metastases
- biopsy
- twice every 28 days for administration of study drug (group A) or once every three weeks (group B).

Also see the answers at ABR E6 and section 4 and appendix C from main ICF.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1 Participant must be >= 18 years at the time of screening.
2 Histologically or cytologically documented NSCLC that is locally advanced or metastatic according to Version 8 of the IASLC Staging Manual in Thoracic Oncology, at the time of study enrolment. Participants with unknown status are not allowed onto the study. Note: A computed tomography or magnetic resonance imaging scan of the brain at baseline is required for all subjects.
3 Where available, a tissue sample obtained after progression on prior anti-PD-(L)1 therapy and <= 3 months prior to randomisation should be provided. Where no such sample is available a tumour sample taken <= 24 months prior to screening is acceptable. Samples should be of sufficient quality to enable assessment of tumour cell PD-L1 expression. Tumour sample must be FFPE, with sufficient material for sectioning preferably 16 slides (5 micron thickness).
If FFPE blocks cannot be provided, then a set of newly cut unstained slides that enable necessary testing should be provided (preferably a minimum of 16 slides). Refer to Section 8.6.1 and the Laboratory Manual for details.
4 Documented tumour cell PD-L1 status as assessed by a central laboratory using the VENTANA SP263 PD-L1 IHC assay prior to randomisation. Participants with unknown PD L1 status are not eligible for study.
5 Documented EGFR and ALK wild-type status as determined at a local laboratory using a well validated, locally approved test. Participants with sensitising EGFR mutations (eg, exon 19 deletion; exon 21 L858R or L861Q; exon 18 G719X; or exon 20 insertion or S768I mutation) or ALK rearrangements are excluded from the study.
6 Tumours harbouring mutations in any of the following genes, if known, as determined by existing local test results: ROS1, RET, MET, BRAF V600, NTRK1 and NTRK2 are excluded.
7 Documented radiological PD whilst on or after receiving the most recent treatment regimen.
8 Eligible for second- or third-line therapy and must have received an anti-PD-(L)1 therapy and a platinum doublet containing therapy for locally advanced or metastatic NSCLC either separately or in combination. Prior durvalumab is acceptable. Refer to exclusion criterion 16 for the requirements for prior anti-PD-(L)1 therapy.
9 Received a minimum of 8 weeks of an anti-PD-(L)1 and at least 2 cycles of platinum doublet containing regimen for locally advanced or metastatic NSCLC (either separately or in combination).
10 Participant must have had a treatment-free interval of >=4 weeks from any prior therapy before the start of study intervention. In addition, the following intervals between the end of the prior treatment and first dose of study intervention must be observed:
(a) Minor surgical procedures (as defined by the investigator): 7

post-operative days
(b) Major surgery (as defined by the investigator): >= 4 weeks
(c) Radiotherapy: >= 4 weeks (participants who receive palliative radiation for non-target tumour lesions need not be subjected to this washout period and can be enrolled immediately).
11 ECOG/WHO performance status of 0 or 1 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing.
At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 TL at baseline and can be accurately measured at baseline as >= 10 mm in the longest diameter (except lymph nodes, which must have short axis >= 15 mm) with CT or MRI and is suitable for accurate repeated measurements. A previously irradiated lesion can be considered a TL if the lesion has clearly progressed.
12 Adequate organ function and marrow reserve (within 7 days of C1D1) as follows:
(a) Haemoglobin >= 9.0 g/dL, with no blood transfusions (packed red blood cells) in the past 28 days
(b) Absolute neutrophil count >= 1.5 × 109/L with no G-CSF administration in the past 28 days
(c) Platelet count >= 100 × 109/L, with no platelet transfusions in the past 28 days
(d) Total bilirubin (TBL) <= 1.5 × ULN or TBL <= 3 × ULN in the presence of documented Gilbert*s syndrome (unconjugated hyperbilirubinemia). Note: Local practice guidelines and/or the local docetaxel label should be used to assess eligibility for the study.
(e) ALT and AST <= 2.5 × ULN; and ALT and AST <= 5 × ULN in case of hepatic metastases
(f) Serum albumin > 30 g/L
(g) Calculated CrCL > 40 mL/min as determined by Cockcroft-Gault (using actual body weight)
Creatinine clearance will be determined using the Cockcroft-Gault formula:
Males:
CrCL (mL/min) = Body weight (kg) × (140 * Age)
72 × serum creatinine (mg/dL)
Females:
CrCL (mL/min) = Body weight (kg) × (140 * Age) × 0.85
72 × serum creatinine (mg/dL)
13 Minimum life expectancy of 12 weeks.
14 Body weight > 30 kg and no cancer-associated cachexia, eg, CTCAE Grade 2 or worse weight loss over the past 3 months.
15 Male or female.
Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
16 Negative pregnancy test (serum test) for WOCBP.
17 Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1%

per year when used consistently and correctly). Women of childbearing potential must agree to use one highly effective method of birth control. They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and remain stable throughout the total duration of the study and for 3 months (Group A) or 6 months (Group B) after the last dose of study intervention. Non-sterilised male partners of a WOCBP must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Refer to Appendix G in the studyprotocol for details.
18 Male participants in Group A must use a condom (with spermicide) with all sexual partners throughout the total duration of the study and for 1 week after the last dose of study intervention. Male participants who intend to be sexually active with a WOCBP partner must be surgically sterile or agree to use one highly effective methods of contraception from the time of screening, throughout the total duration of the study and for 6 months after the last dose of study intervention to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Refer to Appendix G in the studyprotocol for details.
19 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
20 Provision of signed and dated, written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative.

Exclusion criteria

1 Participant with mixed SCLC and NSCLC histology.
2 As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diseases, active infection, active interstitial lung disease/pneumonitis, serious chronic gastrointestinal conditions associated with diarrhoea, psychiatric illness/social situations), history of allogenic organ transplant, which, in the investigator*s opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol.
3 Refractory nausea and vomiting, chronic gastrointestinal disease, inability to swallow a formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of ceralasertib.
4 History of another primary malignancy except for malignancy treated with curative intent with no known active disease >= 5 years before the first dose of study intervention and of low potential risk for recurrence, basal cell carcinoma of the skin, squamous cell carcinoma of the skin or lentigo maligna that has undergone potentially curative therapy or adequately treated carcinoma in situ without evidence of disease.

5 Brain metastases or spinal cord compression unless the participant is stable (asymptomatic, no evidence of new or emerging brain metastases) and off steroids for at least 14 days prior to start of study treatment. Following radiotherapy and/or surgery, participants with brain metastases must wait 4 weeks following the intervention and must confirm stability with imaging before randomisation.
6 Persistent toxicities (CTCAE Grade > 2) caused by previous anticancer therapy; alopecia and vitiligo are excluded toxicities. Participants with Grade >= 2 neuropathy will be evaluated on a case by-case basis after consultation with the study clinical lead. Participants with irreversible toxicity that is not reasonably expected to be exacerbated by study interventions may be included (eg, hearing loss) after consultation with the AstraZeneca study clinical lead.
7 History of ILD/pneumonitis (non-infectious) that required management with steroids.
8 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn*s disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis, granulomatosis with polyangiitis, Graves* disease, rheumatoid arthritis, hypophysitis, uveitis, etc), autoimmune pneumonitis and autoimmune myocarditis). The following are exceptions to this criterion:
(a) Participants with vitiligo or alopecia
(b) Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
(c) Any chronic skin condition that does not require systemic therapy
(d) Participants without active disease in the last 5 years may be included but only after consultation with the study physician
(e) Participants with celiac disease controlled by diet alone
9 History of leptomeningeal carcinomatosis.
10 Known active hepatitis infection, positive HCV antibody, HBsAg or anti-HBc at screening. Participants with a past or resolved HBV infection (defined as the presence of anti HBc and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
11 Known to have tested positive for human immunodeficiency virus (HIV) (positive anti HIV 1 or anti-HIV 2 antibodies) or active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).
12 Investigator judgement of one or more of the following:
(a) Mean resting corrected QT interval > 470 ms, obtained from triplicate ECGs performed at screening.
(b) History of QT prolongation associated with other medications that required discontinuation of that medication, or any current concomitant medication known to prolong the QT interval and cause Torsades de Pointes (TdP).
(c) Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden cardiac death under 40 years of age in first-degree relatives.

13 History of symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted upon discussion with the study clinical lead.
14 Known history of drug or alcohol abuse.
15 Diagnosis of ataxia telangiectasia.
16 Participants who have received more than one line of prior anti PD (L)1, either alone or in any combination, ie, patients who have received two or more prior lines of anti PD (L)1 therapy with a different anti-PD-(L)1 agent in the metastatic setting are excluded with the following exceptions:
(a) Patients who completed treatment with an anti-PD-(L)1 therapy for locally advanced disease, and then were subsequently treated with a different anti-PD-(L)1 therapy for metastatic disease, may be included if they had disease progression on the treatment.
(b) Patients who discontinued treatment with an anti-PD-(L)1 therapy for a reason other than disease progression or significant toxicity and have been retreated with the same anti-PD (L)1 agent again, may be included if they had disease progression on the treatment.
17 (a) Must not have experienced a toxicity that led to permanent discontinuation of the prior anti PD(L)1 therapy.
(b) All AEs while receiving prior anti PD(L)1 therapy must have completely resolved or resolved to baseline prior to screening for this study.
(c) Must not have experienced a Grade >= 3 imAE or an immune-related neurologic or ocular AE of any grade while receiving prior anti PD(L)1 therapy. Note: Participants with an endocrine AE of Grade <= 2 are permitted to enrol if they are stably maintained on appropriate replacement therapy and are asymptomatic.
(d) Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.
18 Participants who have received more than one prior line of platinum-based chemotherapy in metastatic setting.
19 Participants who have received a prior ATR inhibitor.
20 Participants who have received prior docetaxel.
21 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
(a) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
(b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
(c) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
22 Receipt of live attenuated vaccine within 30 days prior to the first dose of

study intervention. Note: Participants, if enrolled, should not receive live vaccine whilst receiving study intervention and up to 180 days after the last dose of study intervention.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-09-2023
Enrollment:	19
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	AZD6738, Ceralasertib
Product type:	Medicine
Brand name:	Imfinzi
Generic name:	MEDI4736, Durvalumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-09-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2023-509429-37-00
EudraCT	EUCTR2022-000493-26-NL
CCMO	NL82148.028.22