A Phase III, double-blind, randomized, placebo-controlled multi-centre, study to assess the efficacy and safety of AZD9291 versus Placebo, in patients with Epidermal Growth Factor Receptor Mutation Positive stage IB-IIIA non-small cell lung carcinoma, following complete tumour resection with or without adjuvant chemotherapy (ADAURA)

Published: 04-08-2015
Last updated: 19-04-2024

To assess the efficacy of AZD9291 compared to placebo as measured by disease free survival (DFS)Protocol v1.0, 4Jun2015, p30

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON45003

Source
ToetsingOnline

Brief title
ADAURA

Condition

- Respiratory tract neoplasms

Synonym
Lungcancer, non-small cell lungcarcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AZD9291, EGFRm, Lung cancer, Non-small Cell Lung Carcinoma

Outcome measures

Primary outcome

Primary outcome of the study is disease free survival by investigator

assessment.

Protocol v1.0, 4Jun2015, p30

Secondary outcome

Secundary outcomes:

- DFS rate at 2, 3 & 5 years

- Overall Survival (OS)

- OS rate at 5 years

- Changes in generic HRQoL as measured by the SF-36

- PK plasma concentrations of AZD9291, and metabolites AZ5104 and AZ7550; and

ratio of metabolite to AZD9291 for each PK sample. PK data from this study will

be analysed using a population PK approach and reported separately to the

Clinical Study Report (CSR). Data from this study may form part of a pooled

analysis with data from other studies.

Protocol v1.0, 4Jun2015, p30

Study description

Background summary

AZD9291 is a potent irreversible inhibitor of both the single mutant EGFRm+ (TKI sensitivity conferring mutation) and double mutant EGFRm+/T790M+ (TKI resistance conferring mutation) receptor forms of EGFR with a significant selectivity margin over wild-type EGFR.
As a result, AZD9291 can effectively block EGFR signaling both in EGFR single mutant cells with activating EGFR mutations and in double mutant cells bearing both the primary EGFR activating and secondary resistance T790M mutation.
AZD9291 is currently under investigation as a treatment option for patients with advanced T790M+NSCLC who have previously failed an EGFR TKI; and for patients with advanced EGFRm+ NSCLC who are treatment naive.

Pre-clinical data provides good evidence to support AZD9291 as a potentially better treatment option for first-line advanced and early stage EGFRm+ NSCLC compared to currently approved EGFR TKIs.

In conclusion, the preclinical and clinical profile of AZD9291 suggest that AZD9291 could offer prolonged disease free survival in the adjuvant EGFRm+ NSCLC setting, and the data are encouraging for the investigation of AZD9291 as an adjuvant treatment for patients with early stage NSCLC who have undergone complete tumor resection.

Protocol v1.0, 4Jun2015, p22-23

Study objective

To assess the efficacy of AZD9291 compared to placebo as measured by disease free survival (DFS)

Protocol v1.0, 4Jun2015, p30

Study design

This is a phase 3, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of AZD9291 versus placebo in patients with stage

IB-IIIA non squamus, non-small cell lung cancer (NSCLC) with a centrally confirmed, common sensitising EGFR mutations (Ex19del and L858R either alone or in combination with other EGFR mutations), who have had complete tumour resection, with or without postoperative adjuvant chemotherapy.

Patients will be randomised 1:1 to receive either AZD9291 or placebo. Patients must have sufficiently recovered from surgery and completed any standard of care adjuvant chemotherapy if applicable prior to randomization. Patients must be randomised within 10 weeks of complete surgical resection if adjuvant chemotherapy was not administered and within 26 weeks if adjuvant chemotherapy was administered.

Protocol v1.0, 4Jun2015, p27

Intervention

Eligible patients will be randomized 1:1 (AZD9291:placebo) (using IVRS) to the below specified treatments:
- AZD9291: 1 tablet of 80 mg once daily
- Placebo: 1 tablet once daily

Protocol v1.0, 4Jun2015, p37

Study burden and risks

Although there can be no certainty of clinical benefit to patients, success of other targeted agents in the adjuvant setting with or without chemotherapy, non-clinical characteristics of AZD9291, the preliminary data of EGFR TKIs in this setting, , the preliminary clinical efficacy and safety data with AZD9291 in the ongoing phase I trial (D5160C00001) all support the notion that EGFR mutation inhibition may be a valid strategy for the adjuvant treatment of completely resected NSCLC tumours.

Specifically the safety profile of AZD9291 in the ongoing phase I trial extended to phase II and ongoing clinical program is favourable with the majority of toxicities being low grade EGFR related adverse events All trials of AZD9291 exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of interstitial lung disease (ILD) or clinically active ILD as this is an uncommon but well documented EGFR-related toxicity. Patients requiring radiotherapy will be excluded from participation due to the potential risk of radiation induced pneumonitis.

In the pre-clinical studies, the principal target organ findings were consistent with inhibition of wild type EGFR (atrophic, inflammatory and degenerative changes in the skin, cornea, gastrointestinal tract and female

reproductive tract). Other target organ findings of potential clinical relevance were seen in the male reproductive tract and male mammary gland. All patients will be assessed for possible known EGFR-related toxicities and detailed information on the management of EGFR-related gastrointestinal, dermatological, and ophthalmologic toxicities is being provided for all AZD9291 studies.

It is therefore, reasonable to evaluate the oral administration of AZD9291 in comparison to placebo as adjuvant therapy in preventing or delaying the recurrence of disease in EGFRm+ NSCLC patients who have undergone complete surgical resection and standard of care chemotherapy where applicable.

Protocol v1.0, 4Jun2015, p26-27

Contacts

Public
Astra Zeneca

Karlebyhus -
Sodertalje SE-15185
NL
Scientific
Astra Zeneca

Karlebyhus -
Sodertalje SE-15185
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Provision of informed consent prior to any study specific procedures, sampling, and analyses
2. Male or female, aged at least 18 years.
3. Histologically confirmed diagnosis of primary non small lung cancer (NSCLC) on predominantly non-squamous histology
4. MRI or CT scan of the brain must be done prior to surgery as it is considered standard of care. Patients in whom this was not done prior to surgery may still be enrolled if appropriate imaging is performed prior to randomization, i.e. MRI or CT of brain.
5. Patients must be classified post-operatively as Stage IB, II or IIIA on the basis of pathologic criteria. Staging will be according to the TNM staging system for lung cancer (7th edition)
6. Confirmation by the central laboratory that the tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations including T790M.
7. Complete surgical resection of the primary NSCLC is mandatory. All gross disease must have been removed at the end of surgery. All surgical margins of resection must be negative for tumour. Resection may be accomplished by open or Video Associated Thoracic Surgery (VATS) techniques
- Refer to section 4.1.2 for additional guidance
8. Complete recovery from surgery and standard post-operative therapy (if applicable) at the time of randomization. Treatment cannot commence within 4 weeks following surgery.
No more than 10 weeks may have elapsed between surgery and randomization for patients who have not received adjuvant chemotherapy; no more than 26 weeks may have elapsed between surgery and randomization for patients who received adjuvant chemotherapy.
- Complete post-operative wound healing must have occurred following any surgery
- For patients who received post-operative adjuvant platinum-based chemotherapy, a minimum of 2 weeks must have elapsed (but no more than 10 weeks) from the last administered dose of chemotherapy to the date of randomization.
Patients must have recovered from all toxicities of prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2 prior platinum therapy related neuropathy.
9. World Health Organization Performance Status of 0 to 1
10. Female patients should be using adequate contraceptive measures, should not be breast feeding, and must have a negative pregnancy test prior to first dose of study drug; or female patients must have an 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 less than50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle-stimulating hormone (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.

- Male patients should be willing to use barrier contraception, i.e., condoms (see section3.8).
11. For inclusion in the optional genetics research study, patients must provide informed consent for genetic research.

Exclusion criteria

1. Previous randomization and treatment in the present study
2. Treatment with any of the following:
- Pre-operative or post-operative or planned radiation therapy for the current lung cancer
- Pre-operative (neo-adjuvant) platinum based or other chemotherapy
- Any prior anticancer therapy
- Prior treatment with neoadjuvant or adjuvant EGFR-TKI at any time
- Major surgery (including primary tumour surgery, excluding placement of vascular access within 4 weeks of the first dose of study drug
- Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 week
prior)
- Treatment with an investigational drug within five half-lives of the compound or any of its related material.
3. Patients who have had only segmentectomies or wedge resections
4. History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumours curatively treated with no evidence of disease for 5 years following the end of treatment.
5. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.
6. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses ; or active infection including hepatitis B, hepatitis C and human
immunodeficiency virus (HIV). Active infection will include any patients receiving intravenous treatment for infection; active hepatitis B infection will, at a minimum, include all patients who are hepatitis B surface antigen positive (HbsAg positive) based on serology assessment. Screening for chronic conditions is not required.
7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of AZD9291.
8. Any of the following cardiac criteria:
- Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value.
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG.
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.

9. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
10. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:.
- Absolute neutrophil count <1.5 x 109 /L.
- Platelet count <100 x 109 /L.
Haemoglobin <90 g/L.
- Alanine aminotransferase (ALT) >2.5x the upper limit of normal (ULN) .
- Aspartate aminotransferase (AST) >2.5xULN.
- Total bilirubin >1.5xULN or >3xULN in the presence of documented Gilbert*s Syndrome (unconjugated hyperbilirubinaemia).
- Creatinine >1.5xULN 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 >1.5xULN.
11. Women who are breast feeding.
12. History of hypersensitivity to active or inactive excipients of AZD9291 or drugs with a similar chemical structure or class to AZD9291.;In addition, the following are considered criteria for exclusion from the exploratory genetic
research only:
1. Prior allogeneic bone marrow transplant.
2. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-03-2016

Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tagrisso
Generic name:	osimertinib

Ethics review

Approved WMO Date:	04-08-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-11-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-01-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date: 20-12-2016

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 22-12-2016

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 23-03-2017

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 06-04-2017

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 25-07-2017

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 26-07-2017

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 19-10-2017

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 06-11-2017

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date: 26-02-2018

Application type: Amendment

Review commission: METC Brabant (Tilburg)

Approved WMO

Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-02-2019
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
EudraCT	EUCTR2015-000662-65-NL
CCMO	NL54024.028.15