Clinical Trial Details (PDF Generation Date :- Fri, 14 Aug 2020 09:38:19 GMT)

CTRI Number	CTRI/2018/10/016042 [Registered on: 16/10/2018] - **Trial Registered Prospectively**
Last Modified On	29/06/2020
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	Study of Osimertinib as maintenance therapy in patients with locally advanced, unresectable Non-Small Cell Lung Cancer whose disease has not progressed following platinum-based chemoradiation therapy
Scientific Title of Study	A Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of osimertinib as maintenance therapy in patients with locally advanced, unresectable EGFR mutation-positive Non-Small Cell Lung Cancer (Stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy (LAURA)

Secondary IDs if Any

Secondary ID	Identifier
D5160C00048 version 1.0 dated 23 Mar 2018	Protocol Number

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	
Designation	
Affiliation	
Address	
Phone	
Fax	
Email	

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
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Details Contact Person (Public Query)

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Source of Monetary or Material Support

Source of Monetary or Material Support
> AstraZeneca AB, 151 85 Södertälje, Sweden

Primary Sponsor

Primary Sponsor Details	
Name	AstraZeneca AB
Address	151 85 Sodertalje Sweden
Type of Sponsor	Pharmaceutical industry-Global

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

List of Countries
Argentina
China
India
Japan
Republic of Korea
Spain
Taiwan
Thailand
Turkey
United States of America
Viet Nam

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
Dr Sushant Mittal	Action Cancer Hospital	Ground floor, Dept. of Medical Oncology A4, Paschim Vihar PIN-110063 West DELHI	01149222222 01145024287 sushantmittal80@gmail.com
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Dr Kartikeya Jain	Himalaya Cancer Hospital & Research Institute,	Third floor, Dept. of Medical Oncology #4 Vinod Baugh, Jetalpur bridge, Alkapuri - 390007 Vadodara GUJARAT	0265-6542151 jainkartikeya@rocketmail.com
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DrBivas Biswas	Tata Medical Centre Kolkata	Department of Medical Oncology 14-MAR (EW), New Town, Rajarhat Kolkata WEST BENGAL	9830922005 bivasbiswas@gmail.com
Dr Kiran Ashok Kattimani	The Karnataka Cancer Therapy & Research Institute	First floor, Dept. of Medical Oncology, Padmashree Dr. R. B. Patil Cancer Hospital Navanagar, Hubli-580025 Dharwad KARNATAKA	0836-2228217 0836-2323167 dr_kattimani@yahoo.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Action Cancer Hospital Ethics Committee, Action Cancer Hospital	Approved	03/10/2018	No
Artemis Health Sciences Institutional Ethics Committee	Approved	20/10/2018	No
Institutional Ethics Committee H. M. Patel Centre for Medical Care and Education	Approved	19/11/2018	No

Institutional Ethics Committee Shree Himalaya Cancer Hospital & Research Institute	Approved	24/09/2018	No
Institutional Ethics Committee,The Karnataka Cancer Therapy & Research Institute	Approved	13/11/2018	No
Institutional Review Board (IRB) Rajiv Gandhi Cancer Institute and Research Centre (RGCI & RC)	Approved	21/12/2018	No
Manavata Clinical Research Institute Ethics Committee	Approved	09/04/2019	No
Shetty's Hospital Ethics Committee	Approved	20/10/2018	No
Sri Venkateshwara Hospital Ethics Committee	Approved	15/10/2018	No
Tata Medical centre-Institutional Review Board	Approved	14/10/2019	No

Regulatory Clearance Status from DCGI

Status	Date
Approved/Obtained	27/08/2018

Health Condition / Problems Studied

Health Type	Condition
Patients	Malignant neoplasm of unspecifiedpart of bronchus or lung
Patients	Malignant neoplasm of unspecifiedpart of bronchus or lung

Intervention / Comparator Agent

Type	Name	Details
Intervention	Osimertinib oral once a day, until objective radiological disease progression as defined by RECIST v1.1	Patients will be in a 2:1 ratio to either Osimertinib or placebo
Comparator Agent	Placebo oral once a day, until objective radiological disease progression as defined by RECIST v1.1	Patients will be in a 2:1 ratio to either Osimertinib or placebo

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	99.00 Year(s)
Gender	Both
Details	1.Male and Female patient must be aged at least 18 years. 2.Provision of signed and dated written informed consent for Part I screening form prior to any mandatory provision of tumor samples for testing of EGFR mutation status. 3.Patients with histologically documented NSCLC of predominantly non-squamous pathology who present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the International Association for the Study of Lung Cancer [IASLC] Staging Manual in Thoracic Oncology).

Part II Screening:
Part II screening applies to:
(i)patients that have a pre-existing local positive (Exon 19 Deletion or L858R) cobas® EGFR Mutation Test v2 (Roche Diagnostics) in a CLIA-certified (USA sites) or an accredited local laboratory (sites outside of the USA) conducted according to the cobas® EGFR Mutation Test v2 instructions for use or (ii) patients who completed Part I screening and have centrally confirmed EGFR mutation (Ex19 Deletion or L858R) positive NSCLC.
4.Provision of signed and dated, written informed consent form for the main study prior to any mandatory study specific procedures, sampling, and analyses.
5.The tumor harbours one of the two common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations, assessed by cobas® EGFR Mutation Test v2 (Roche Diagnostics) in a CLIA certified (USA sites) or an accredited local laboratory (sites outside of the USA) or by central testing.
6.Patients must not have had disease progression during or following definitive platinum based, chemoradiation therapy.
7.Patients must have received either concurrent chemoradiation or sequential chemoradiation regimens as defined below;
-CCRT- Patients must have received at least 2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum–based chemotherapy) concurrent with radiation therapy, which must be completed ?6 weeks prior to randomization. The final chemotherapy cycle must end prior to, or concurrently with, the final dose of radiation. (A final cycle of platinum and pemetrexed doublet is permitted up to 3 days after the last dose of radiation). Consolidation chemotherapy after radiation is not permitted but administration of chemotherapy prior to CCRT is permitted
-SCRT- SCRT is defined as chemotherapy followed by radiation therapy and not radiation therapy followed by chemotherapy. Patients must have received at least 2 cycles of platinum based chemotherapy prior to radiation treatment, which must be completed ?6 weeks prior to randomization. Consolidation chemotherapy after radiation is not permitted
8.The platinum-based chemotherapy regimen must contain one of the following agents: etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, or pemetrexed, according to the local standard of care regimens. Gemcitabine is permitted if used prior to radiation but not with radiation.
9.Patients must have received a total dose of radiation of 60 Gy ±10% (54 to 66 Gy) as part of the chemoradiation therapy in order to be randomized. It is recommended but not required that patients eligible for randomization have a
-Mean lung dose y values.br/ -Absolute neutrophil count 1.5 x 109/Lbr/ -Platelet count 100 x 109/Lbr/ -Haemoglobin 90 g/Lbr/ -Alanine aminotransferase (ALT) 2.5x the upper limit of normal (ULN)br/ -Aspartate aminotransferase (AST) 2.5x ULNbr/ -Total bilirubin 1.5x ULN or 3x ULN in the presence of documented Gilbert’s Syndrome (unconjugated hyperbilirubinemia)br/ -Creatinine 1.5x 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 1.5xULNbr/
7.History of other malignancies, except: adequately treated non-melanoma skin cancer or lentigo maligna , curatively treated in-situ cancer, or other solid tumors curatively treated with no evidence of disease for > 5 years following the end of treatment and which, in the opinionof the treating physician, do not have a substantial risk of recurrence of the prior malignancy.

	8.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 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. 9.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. Prior/concomitant therapy; 10.Prior treatment with any prior chemotherapy, radiation therapy, immunotherapy or investigational agents for NSCLC outside of that received in the definitive setting for Stage III disease (chemotherapy and radiotherapy in SCRT and CCRT regimens is allowed for treatment of Stage III disease). Prior surgical resection (i.e. stage I or II) is permitted. 11.Prior treatment with EGFR-TKI therapy. 12.Major surgery as defined by the investigator within 4 weeks of the first dose of study drug. 13.Patients currently receiving (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 weeks prior to receiving the first dose of study drug). 14.Participation in another clinical study with an investigational product during the 4 weeks prior to Day 1. Patients in the follow-up period of an interventional study are permitted. 15.Patient with involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). 16.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. 17.Patient was previously randomized in the present study. 18.For female patients only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding. 19.Contraindication to MRI, including but not limited to, claustrophobia, pace makers, metal implants, intracranial surgical clips and metal foreign bodies. 20.History of hypersensitive to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib. 21.Prior allogeneic bone marrow transplant. 22.Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

Method of Generating Random Sequence	Stratified block randomization
Method of Concealment	Centralized
Blinding/Masking	Participant and Investigator Blinded

Primary Outcome

Outcome	Timepoints
To assess the efficacy of osimertinib treatment compared with placebo as measured by progression free survival (PFS)	Overall Survival (OS) (Time frame-Approximately 5 years)

PFS using BICR assessment according to RECIST v1.1 Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1	

Secondary Outcome

Outcome	Timepoints
Secondary objectives To assess the efficacy of osimertinib treatment compared with placebo by assessment of PFS in patients with: EGFR Ex19del or L858R mutation EGFRm plus Ex19del or L858R detectable in plasma-derived ctDNA	Overall Survival (OS) (Time frame-Approximately 5 years)
To assess the efficacy of osimertinib versus placebo on CNS PFS	Overall Survival (OS) (Time frame-Approximately 5 years)
To assess the efficacy of osimertinib versus placebo on CNS PFS	Overall Survival (OS) (Time frame-Approximately 5 years)
To further assess the efficacy of osimertinib compared to placebo post progression	Overall Survival (OS) (Time frame-Approximately 5 years)
To assess disease-related symptoms and health-related QoL in patients treated with osimertinib compared with placebo	Overall Survival (OS) (Time frame-Approximately 5 years)
To assess the safety and tolerability profile of osimertinib compared with placebo	Overall Survival (OS) (Time frame-Approximately 5 years)
To assess the PK of osimertinib	Overall Survival (OS) (Time frame-Approximately 5 years)
Exploratory objectives: To assess potential treatment-related adverse effects in patients treated with osimertinib compared with placebo using PRO-CTCAE	Overall Survival (OS) (Time frame-Approximately 5 years)
To assess the patients' overall impression of the severity of their cancer symptoms using PGIS	Overall Survival (OS) (Time frame-Approximately 5 years)
To compare osimertinib treatment with placebo treatment on health state utility	Overall Survival (OS) (Time frame-Approximately 5 years)
To compare health resource use associated with osimertinib treatment versus placebo	Overall Survival (OS) (Time frame-Approximately 5 years)
To investigate the relationship between osimertinib (and metabolite) PK and selected endpoints (which may include efficacy, safety and/or PRO), where deemed appropriate	Overall Survival (OS) (Time frame-Approximately 5 years)

Target Sample Size	**Total Sample Size=**200 **Sample Size from India=**18 **Final Enrollment numbers achieved (Total)=**Applicable only for Completed/Terminated trials **Final Enrollment numbers achieved (India)=**Applicable only for Completed/Terminated trials
Phase of Trial	Phase 3
Date of First Enrollment (India)	22/10/2018
Date of First Enrollment (Global)	01/08/2018
Estimated Duration of Trial	**Years=**6 **Months=**0 **Days=**0

Recruitment Status of Trial (Global)	Open to Recruitment
Recruitment Status of Trial (India)	Open to Recruitment
Publication Details	not yet
Brief Summary	This is a Phase III, randomized, double-blind, placebo-controlled, multicenter international study assessing the efficacy and safety of osimertinib, as maintenance therapy in patients with locally advanced, unresectable epidermal growth factor receptor (EGFR) mutation positive non-small cell lung cancer (Stage III), whose disease has not progressed following definitive platinum based- chemoradiation therapy.Patients will be randomized in a 2:1 ratio (osimertinib to placebo). If fewer than 40 patients have been recruited in mainland China, recruitment will continue in mainland China until approximately 40 patients have been randomized. Osimertinib 80mg po QD until objective radiological disease progression per (RECIST) v1.1 which is confirmed by BICR or until another treatment discontinuation criterion is met. Matching placebo 80 mg po QD until objective radiological disease progression per (RECIST) v1.1 which is confirmed by BICR or until another treatment discontinuation criterion is met.Patients randomized will have achieved a complete response (CR), partial response (PR), or have stable disease (SD) following definitive, platinum-based, chemoradiation. Randomization will be stratified by: sequence of chemoradiation (concurrent versus sequential), disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) and will also include China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity versus enrolled at Non-Chinese site or patient declaring themselves of non-Chinese ethnicity) as a stratification factor to allow separate randomization for the purposes of reporting in China.In order to reflect global clinical practice, recruitment will be monitored on an ongoing basis and will be managed to ensure that the majority (?60%) of patients entering the study have received prior CCRT. Study entry is permitted based on detection of Exon 19 deletion and/or L858R mutation based on central tissue EGFR testing using the cobas® EGFR Mutation Test v2, or from a pre-existing local EGFR test result obtained using the cobas® EGFR MutationTest v2 from a CLIA-certified (USA sites) or an local laboratory (sites outside of the USA).