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Osimertinib

<oz-ee-mer-ti-nib>



Design of the NeoADAURA clinical study: Osimertinib treatment before surgery in patients with non-small cell lung cancer with a mutation in the epidermal growth factor receptor gene

Date of summary: June 2021

Study number: NCT04351555

Study dates:

- **Study start date:** December 2020;
- **estimated date for completing collection of data for the main aim of the study:** mid-2024;
- **estimated study end date:** mid-2029

Full title of this article: Neoadjuvant osimertinib with/without chemotherapy vs chemotherapy alone for *EGFR*-mutated resectable NSCLC: NeoADAURA

Key words:

Osimertinib	Treatment before surgery
<i>EGFR</i> gene	Personalized treatment
Non-small cell lung cancer	Lay summary
Surgery	Plain language summary
Chemotherapy	

Who should read this article?

- Patients and their families, patient advocates, caregivers and healthcare professionals, including people who are helping someone to find the best treatment for their diagnosis.

Why is the NeoADAURA study being carried out?

What is *EGFR*-mutated NSCLC?

- Lung cancer occurs when there is an abnormal growth of cells (known as a tumor) in the lungs. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.
- Some patients with NSCLC have tumors with a mutation in the *epidermal growth factor receptor (EGFR)* gene. This type of lung cancer is called *EGFR*-mutated NSCLC and can be identified using a test for *EGFR* gene mutations on the tumor tissue.
 - When *EGFR* is written in italics, it means the *EGFR* gene.
 - The EGFR protein is written without italics. It is a receptor at the surface of the cells in the human body that can regulate how cells grow and divide.
- *EGFR* mutations can cause lung cancer tumors to grow faster, due to a change in the receptor functioning.
- Some ethnic groups are more predisposed to having *EGFR* mutations than others; they are found in up to approximately 50% of all Asian patients with NSCLC, and at lower rates in patients with NSCLC from other parts of the world.
- Testing tumors for *EGFR* mutations at diagnosis can help ensure patients receive the most appropriate treatment for their tumor.
- NSCLC is divided into different categories (stage I, II, III, or IV) depending on the size of the tumor and how much the cancer has spread. According to version 8 of the Cancer Staging Manual from the International Association for the Study of Lung Cancer:

- Stage I is when the cancer is small and has not spread to lymph nodes (glands that filter out harmful substances) or distant parts of the body. At stage IA the cancer is smaller than 3 cm, and at stage IB the cancer is >3 to ≤4 cm in size.
- Stage IIA/B is when the cancer is larger than 4 cm or has spread to some nearby areas, such as nearby lymph nodes.
- Stage IIIA/B/C is when the cancer has grown and spread to nearby areas, such as the lymph nodes (this is known as regional metastasis).
- Stage IV is when the cancer, which can be of any size, has spread to another part of the body (this spreading is called metastasis).
- The stage of a patient's cancer will determine the type of treatment or treatments they receive.
 - Patients with stage I and II and some patients with stage III NSCLC, who altogether comprise around one third of all patients with NSCLC, can have surgery to remove their tumors (resectable NSCLC).
 - Stage IIIA/B tumors can vary a great deal in size, placement, and how they have spread to the lymph nodes so treatment may vary. For patients with resectable stage IIIA/B-N2 NSCLC, surgery combined with other treatments may be the best option.
 - N2 means that the cancer has spread to the lymph nodes near to the cancer in the lung, which can allow the cancer to spread to lymph nodes in other parts of the body.
 - Patients with stage II and III and some with stage IB disease can also receive chemotherapy after surgery to help kill any small traces of cancer (called 'micrometastases') that may remain after surgery.
 - Chemotherapy is a cancer treatment where a chemical agent is used to kill cancer cells at specific stages of a cell's lifecycle, however it cannot differentiate between cancer cells and healthy cells. Thus, it is not a targeted treatment.

Why are new treatments needed for *EGFR*-mutated NSCLC?

- Unfortunately, in many patients with resectable *EGFR*-mutated NSCLC, the cancer can still grow back after surgery.
 - In some cases, micrometastases may have already detached from the tumor and spread to other parts of the body before surgery.
 - For example, one study has shown that two years after surgery, only 52% of patients with stage IB–IIIA disease were alive and cancer-free. The cancer can even grow back after receiving post-surgery chemotherapy.
 - In another study, among patients with stage II–IIIA disease receiving chemotherapy after surgery, only 33% and 23% were alive and cancer-free after three and five years, respectively.
 - New and improved therapies are therefore needed for patients with resectable *EGFR*-mutated NSCLC to stop cancer returning after surgery. A targeted treatment for cancer uses drugs to target specific genes or proteins that are involved in the growth and survival of cancer cells.
- Currently, some but not all patients are given anti-cancer treatments after surgery.
 - However, it might be better to receive an anti-cancer treatment before surgery to try and shrink the tumor and remove any micrometastases in other parts of the body, so the cancer is less likely to grow back.
- Another type of targeted treatment called 'immunotherapy' has been assessed in clinical trials, either alone or in combination with chemotherapy, before surgery, for patients with resectable NSCLC.
 - Immunotherapy helps the immune system to fight the cancer.
 - However, these treatments appear to have limited benefit for patients with *EGFR*-mutated tumors and therefore a different approach is needed.

What is osimertinib?

- Osimertinib (also called TAGRISSO®) is a type of medication called an *EGFR*-tyrosine kinase inhibitor and is used to treat *EGFR*-mutated NSCLC.
 - *EGFR*-tyrosine kinase inhibitors work by slowing down, preventing, or stopping the growth of *EGFR*-mutated NSCLC tumors by blocking the activity of the *EGFR* protein on the surface of cancer cells.
 - Unlike chemotherapy, osimertinib is a personalized (targeted) treatment option.
- Osimertinib is currently approved by the FDA in the US, the EMA in Europe, and in many other countries globally for treating patients with *EGFR*-mutated NSCLC that has spread by metastasis to other parts of the body (stage IV disease).
- Recently, results from the ADAURA study showed that osimertinib given after surgery to patients with stage IB–IIIA *EGFR*-mutated NSCLC resulted in longer cancer-free survival compared with placebo (a dummy drug that does not contain an active substance, e.g. made of starch or sugar).
 - At two years after the start of treatment, 89% of patients treated with osimertinib were alive and cancer-free compared with 52% of patients treated with placebo.
 - In the United States, China, the EU, and in many other countries globally osimertinib has been recently approved for treating patients with resectable *EGFR*-mutated NSCLC after surgery.
- The positive results from the ADAURA study, together with the initial results from trials of other *EGFR*-tyrosine kinase inhibitors given before surgery, support the concept that osimertinib given before surgery may benefit patients with resectable *EGFR*-mutated NSCLC.

What is the NeoADAURA clinical trial looking at?

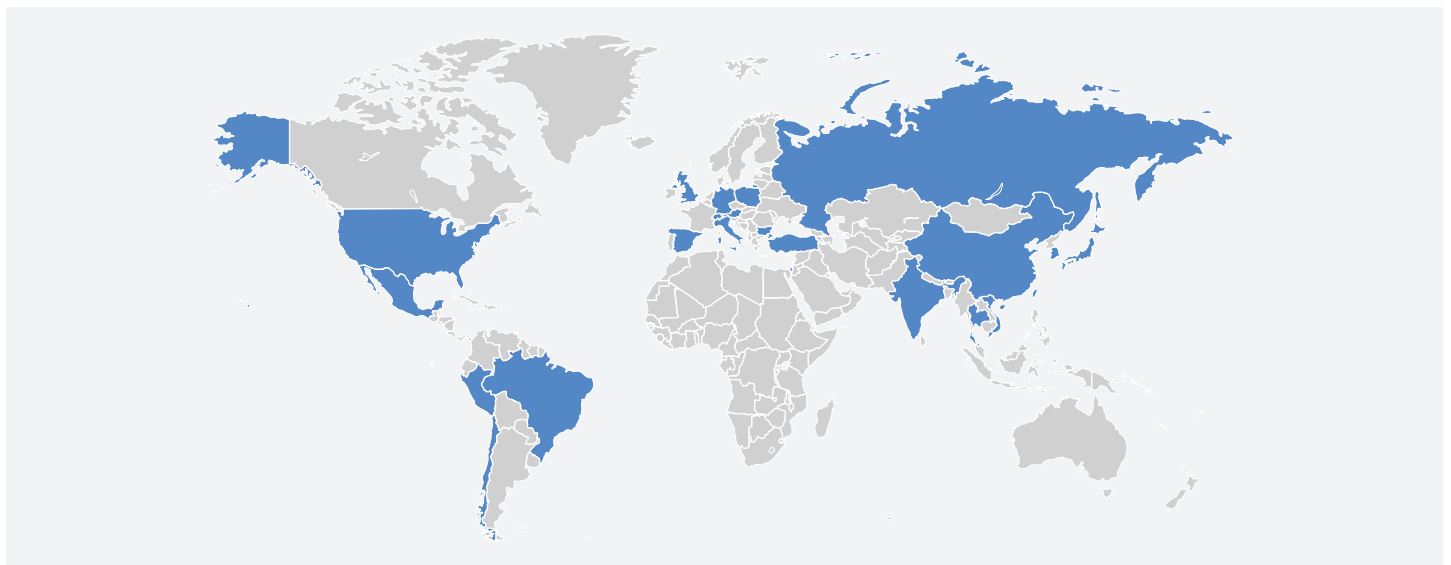
- The NeoADAURA study is looking at how effective osimertinib (alone or in combination with chemotherapy) is in patients with resectable *EGFR*-mutated NSCLC, when given to patients **before** their lung tumors are completely removed by surgery.
 - The aim is to investigate whether this treatment can help stop or shrink micrometastases in the body, and therefore prevent the cancer from growing back in the future.
 - The reason why some patients are receiving osimertinib together with chemotherapy before surgery is to compare if this treatment could be more effective than osimertinib on its own in resectable *EGFR*-mutated NSCLC. This choice is supported by previous studies suggesting that it may be effective to combine an *EGFR*-tyrosine kinase inhibitor with chemotherapy in patients with *EGFR*-mutated NSCLC that has spread to other parts of the body.
- The safety of osimertinib treatment given before surgery and the patients' quality of life will also be assessed.
- The first patient started the study in December 2020; more patients will be included in the future and the first results addressing the main aim of this study are expected to be available in mid-2024. The study is expected to end in mid-2029.
- Here, we provide an overview of the design and plan of this study.

Who is being included in the study?

- Patients aged ≥18 years (or ≥20 years if in Japan).
- Patients with *EGFR*-mutated NSCLC, that is, people who have had a positive test for an *EGFR* gene mutation on their tumor tissue.
- Patients with NSCLC that can be completely removed by surgery, as assessed by the surgeon.
- Patients with stage IIA, IIB, IIIA, or IIIB N2 disease (according to version 8 of the Cancer Staging Manual from the International Association for the Study of Lung Cancer).
- Patients with a fitness category score (called a performance score) of 0 (fully active) or 1 (able to walk but may not be able to do heavy physical activity).
- Patients who have not had:
 - Previous anti-cancer treatment for NSCLC
 - A condition called interstitial lung disease, which causes scarring and stiffness of the lungs and breathing difficulties
 - Ongoing severe diseases that may prevent surgery or other anti-cancer treatments.
- It is estimated that about 350 patients will start the NeoADAURA study.

Where is the study taking place?

The NeoADAURA study is taking place at 184 hospitals / clinics in 23 countries:



Austria
Brazil
Bulgaria
Chile

China
Germany
India
Israel

Italy
Japan
Mexico
Peru

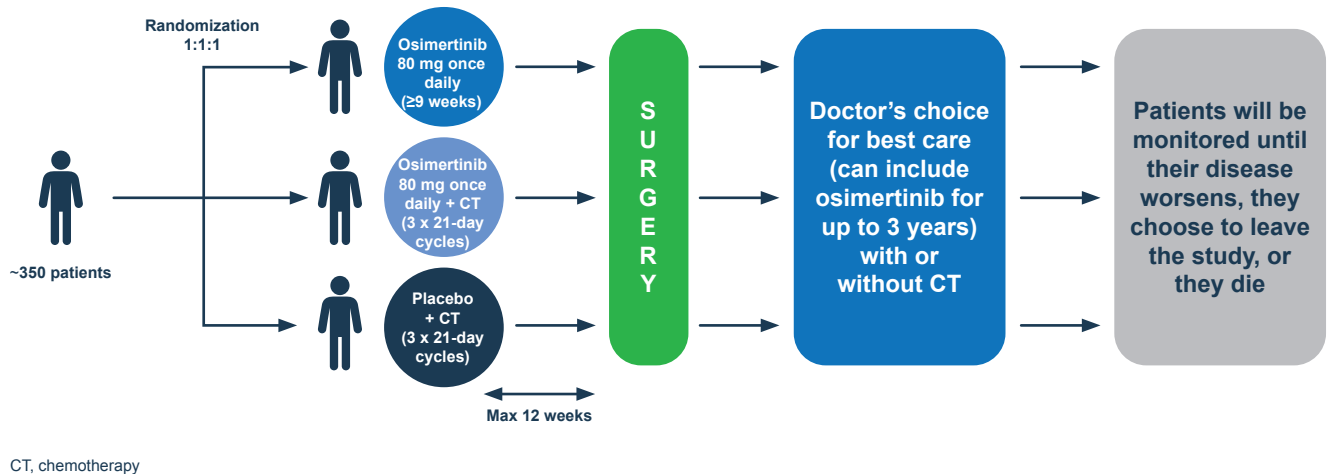
Poland
Russian Federation
Republic of Korea
Spain

Switzerland
Taiwan
Thailand
Turkey

United Kingdom
United States
Vietnam

What medications are patients receiving in the NeoADAURA study?

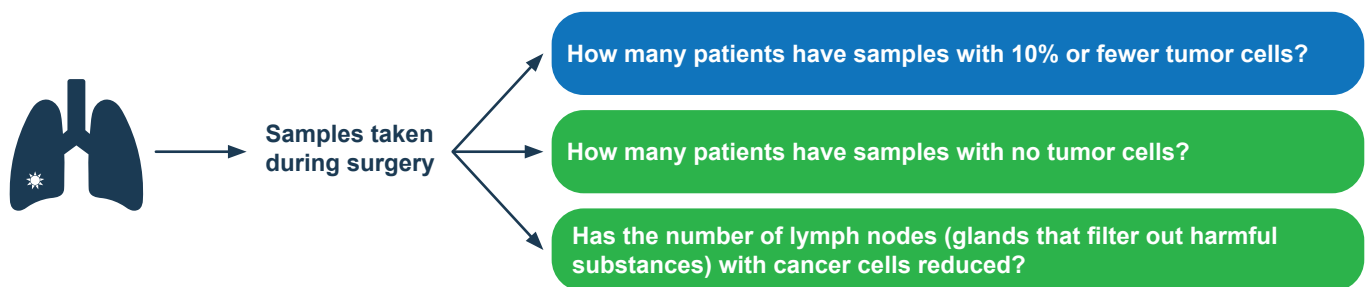
- Patients will receive one of three treatments: either osimertinib on its own, osimertinib with chemotherapy, or placebo with chemotherapy.
 - Osimertinib is taken once daily by mouth as a tablet.
- Osimertinib will be given for a minimum of nine weeks and chemotherapy will consist of three 21-day cycles.
- As soon as possible after completing this treatment, patients will have surgery to remove their lung tumor.
- After surgery, the patient and their doctor will decide if further treatment is needed, which could include osimertinib with or without chemotherapy for up to 3 years.
- After surgery, all patients will be monitored by their doctor over time, to be able to study the effect of the treatments.



What is the study measuring?

- The following data will be collected in the NeoADAURA study to see if osimertinib treatment with or without chemotherapy before surgery has a better outcome for the patient than chemotherapy alone before surgery:

The main objective of this study is to assess samples at the time of surgery:



Other key objectives of this study are to collect information from the start of the study:

Length of time that patients remain alive without cancer progression or cancer recurrence and cancer-free without needing other treatments (event-free survival)

Length of time that patients remain alive and cancer-free (disease-free survival)

Length of time that patients remain alive (overall survival)

- The effect of treatment on the patient's well-being and their everyday life, as well as side effects, will also be measured.
 - Patients will be asked about side effects at each study visit.
 - Patients will be regularly asked to fill out questionnaires for patients with cancer to report how they feel and how they are coping with everyday life.
- Blood samples taken throughout the study will be used to measure the number of tumor cells that may be circulating in the blood of some patients – these small amounts of leftover tumor cells are too small to detect with usual methods, e.g. using a scan to see inside the body or a microscope, but can be a major cause of cancer re-growth. The presence of these tumor cells in the blood will be compared with the patients' response to treatment before and after surgery to see if there is a relationship.

Why is the NeoADAURA study important?

- The results from the NeoADAURA study will help doctors to understand which treatment (osimertinib with chemotherapy, osimertinib without chemotherapy, or chemotherapy alone) is most beneficial for patients with resectable *EGFR*-mutated NSCLC before they have surgery.
 - The results will also help doctors understand which treatment helps reduce the likelihood of the cancer recurring.
 - As patients will have different stages of disease in the study, the data will help doctors understand how well each treatment works for patients with different stages of disease.
- Patients who participate in the study are treated according to the best current standard of care and may benefit from the study treatments they receive.

What are the next steps for this study?

- Patients with *EGFR*-mutated NSCLC will start treatment in the NeoADAURA study and doctors will monitor the patients and collect data to assess the effect of osimertinib, with or without chemotherapy, or chemotherapy alone before surgery to remove their lung tumors.

Who is sponsoring this study?

- This study is funded by AstraZeneca, the manufacturer of osimertinib.

Further information

The original article is published here: Tsuboi M et al. *Future Oncol.* 2021; doi: 10.2217/fon-2021-0549

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- The original article can be accessed for free.
- NeoADAURA is registered with:
 - Clinicaltrials.gov, registration number: NCT04351555 (available from: <https://clinicaltrials.gov/ct2/show/NCT04351555>)
 - EU Clinical Trials register: type the EudraCT identifier 2020-000058-89 into the search field at www.clinicaltrialsregister.eu/ctr-search
- If you are a study participant and have questions about this study, please speak with the doctor or staff at your study center.
- Patients should ask their healthcare providers for more information about the benefits and risks of any treatment.
- More information about clinical trials in general can be found at: <https://www.clinicaltrials.gov/ct2/about-studies/learn>
- For more detail on non-small cell lung cancer and its treatment, please see: <https://www.esmo.org/for-patients/patient-guides/non-small-cell-lung-cancer>

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