



ETOP 7-14 NICHE

Afatinib in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations

- 1) This template Patient Information Sheet and Informed Consent has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the Declaration of Helsinki.
- 2) This template can be edited to incorporate information specific to your institution. Please forward the edited version to the ETOP Coordinating Office for approval. Submit to the Ethics Committee/IRB only after approval by the ETOP Coordinating Office. The final version must have received the IRB/Local Ethics Committee approval in advance of use.
- 3) Following the ICH-GCP guidelines, the Informed Consent should contain information about the following items:
 - a) The trial involves research
 - b) Purpose of the trial
 - c) Trial treatment(s) and the probability of random assignment
 - d) The subject's responsibilities
 - e) The aspects of the trial that are experimental
 - f) Risks
 - g) Benefits
 - h) Alternative treatments available
 - i) Compensation/expenses
 - j) Subject's participation is voluntary/right to withdraw
 - k) Confidentiality
 - l) Information about course of the trial
 - m) Circumstance under which trial may be terminated
 - n) Contact persons for further information or in case of injury
 - o) The approximate number of subjects involved in the trial
 - p) Duration of subject's participation in the trial
 - q) Version number and date
- 4) This template has been designed to cover the above items. If the IRB/Local Ethics Committee requires modifications, none of the above items should be completely excluded, nor should the meaning of the highlighted areas be modified. Such modifications must be submitted to ETOP for approval.
- 5) In order to assist in the preparation of your customized version, an electronic file in MS Word will be distributed via e-mail to all Principal Investigators or ETOP members may download it from the ETOP web site (www.etop-eu.org).

PATIENT INFORMATION SHEET AND INFORMED CONSENT APPENDIX 1

ETOP PATIENT INFORMATION SHEET FOR CLINICAL RESEARCH

Dear patient,

You are being asked to participate in a clinical research study. The doctors at different centers of the European Thoracic Oncology Platform (ETOP) and in other cooperative groups or centers throughout the world study the nature of lung cancer and attempt to develop improved methods of diagnosis and treatment. This is called clinical research. In order to decide whether or not you should agree to be part of this research study you should understand enough about its risks and benefits to make an informed judgment. Your participation in this research study is entirely voluntary and you will be given sufficient time to decide whether you wish to participate. This process is known as Informed Consent.

This Patient Information Sheet gives detailed information about the research study, which your doctor will discuss with you. Once you understand the study, if you wish to participate, you will be asked to sign the Patient Informed Consent. You will have a copy of this document and of the Patient Informed Consent to keep as a record.

The clinical research study being proposed to you is:

ETOP 7-14 NICHE

Afatinib in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations

PURPOSE OF THE RESEARCH STUDY

You have been diagnosed with a type of lung cancer that is *called “non small cell lung cancer (NSCLC)”*. Your lung cancer has recently relapsed despite previous treatment with chemotherapy. Relapsed means that, despite treatment, the cancer is growing. Your doctor has decided that further treatment of your cancer is necessary. Previous clinical studies of NSCLC have shown that patients with tumors harboring specific gene mutations (changes) in the epithelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) showed better results after treatment with tyrosine kinase inhibitors (TKI), like afatinib (tradename Giotrif®) , compared with classical treatment with chemotherapy. The treatment with TKI has become a new standard-of-care for patient with advanced lung cancer and EGFR or ALK changes. Several novel mutations, which are candidates as targets for specific medication have been discovered. Human epidermal growth factor 2 (HER2, erbB-2/neu) is a protein of the so called ErbB family (including HER2 [ErbB2], ErbB3 and ErbB4). These proteins are involved in the growth and spread of cancer cells. Mutations in *HER2* are found in about 2% of the NSCLC.

Afatinib works by blocking the activity of the ErbB family proteins and can inhibit growth and spread of cancer cells.

The aim of the current study is to investigate the control of disease in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations as well as the safety and tolerability (how severe the side effects are) of the treatment with afatinib.

Afatinib is approved by the European and the Swiss Medicines Agencies for the treatment of adult patients with a specific type of cancer of the lung (non-small cell lung cancer) that is identified by a change (mutation) in the gene for EGFR as first treatment or if prior chemotherapy treatment has been insufficient.

A total of 22 patients from centers around Europe are expected to be enrolled in this study over a period of 24 months. In *country* it is planned that *xx* patients will take part. All patients will be treated in the same way. The study will take approximately 40 months to be completed.

This clinical trial is conducted according to the applicable national laws and international guidelines. The trial has been approved by the independent Ethics Committee concerned *insert name of the Ethics Committee*.

DESCRIPTION OF THE CLINICAL RESEARCH STUDY

If you decide to participate in the study and meet the criteria to take part in the study, you will receive the following treatment:

Afatinib 40 mg orally, daily. You will take afatinib tablets every day. Tablets should be taken at a fixed time each day and at least 1 hour before or 3 hours after the ingestion of food.

Inpatient admission into a hospital is not envisaged, but can potentially become necessary.

In order to determine if you can participate in this trial a piece of your tumor, that has been removed at the time of diagnosis, must be available for later central review of *HER2* mutation

You will have a full medical history taken, physical examination, radiological and lab workout performed at the time you enter the study. If you are a female of child-bearing potential, a pregnancy test will be done.

During the study treatment, you must visit your treating physician every 3 weeks for the first 12 weeks, then every 4 weeks for a physical examination. Please take with you all empty, full and partly used boxes of afatinib tablets. Routine blood and urine analyses including liver and kidney function will be carried out every 3 or 4 weeks respectively, as part of standard medical routine. If you develop side effects, more frequent examinations may be necessary.

Your physician will document your general condition and all hospital stays during the clinical trial. He/she will similarly ask you about all side effects, which you experienced and about all medications or treatments, which you received since your last visit.

To determine the status of your lung cancer and effects from the treatment, radiological examinations (computer tomography (CT) of the chest) will be conducted every 6 weeks (week 6 and 12) and later every 8 weeks until your tumour grows

again. These examinations are carried out as part of medical routine and can be performed more frequently, if your treating physician considers this appropriate.

Your doctor may suggest other tests, such as CT of the brain. The regular doctor's visits are part of your standard medical care and are handled the same way as if you did not take part in the study.

If you participate in the study, you should follow the instructions of your treating physician, follow the schedule of treatment visits, record on the patient diary the afatinib tablets taken, inform your physician of any new signs and symptoms, and any non-study medication you take.

VOLUNTARY PARTICIPATION/RIGHT TO REFUSE OR WITHDRAW

Your participation in this research study is entirely voluntary. If you decide not to participate in the study, this will not affect your medical care in any way. If you begin the study, you will have the right to withdraw at any time without giving any reason. This will not affect your future medical assistance. You will be asked to have a final examination before you withdraw and you will be advised for other available care which suits your needs and medical condition. If you should withdraw, data already collected until then will be used for analysis.

RISKS AND DISCOMFORTS

While you receive protocol treatment, you are at risk of side effects. Your physician will be checking you closely to see if any of the side effects are occurring. You should report any side effect or symptom that you experience to your physician. Other drugs may be given to make some of these side effects less serious and uncomfortable.

Afatinib side effects:

Very common (≥ 10%):

- Diarrhoea
- Skin rash
- Mouth sores and inflammation
- Nail infection
- Decreased appetite
- Bleeding from the nose

Common (1 – 10%):

- Pain, redness, swelling or peeling of the skin of your hands and feet
- Increased levels of the liver enzymes in blood tests.
- Inflammation of the lining of the bladder
- Abnormal taste sensations (dysgeusia)
- Stomach pain, indigestion, heartburn
- Lip inflammation
- Decreased weight
- Runny nose
- Muscle spasms
- Fever

Rare (< 1%)

- Inflammation of the lungs called "interstitial lung disease"
- Eye irritation or inflammation

Your physician will be checking you closely to see if any of these side effects are occurring. Your doctor may prescribe medication to keep these side effects under control.

You should tell your doctor:

- If you have diarrhoea lasting more than 2 days. Diarrhoea may lead to fluid loss (common, may affect up to 1 in 10 people), low blood potassium (common) and worsening kidney function (common). Diarrhoea can be treated. At the first signs of diarrhoea drink plenty of fluids. You should have antidiarrhoeal medicine available prior to taking afatinib.
- If a rash starts. If treatment for rash is not working and the rash is getting more severe (for example, you have peeling or blistering of the skin) you should notify your doctor immediately, since your doctor may decide to stop your treatment with afatinib. Rash may occur or worsen in areas exposed to sun. Sun protection with protective clothing and sunscreen is recommended.
- If you develop new or sudden worsening of shortness of breath, possibly with a cough or fever.
- If you have sudden onset or worsening of eye symptoms such as pain or redness or dry eye.

Pregnancy/Birth Control:

All women who participate in the trial and are able to become pregnant must use effective contraception while they receive study medication.

You will not be allowed to enter this study if you are pregnant, plan to become pregnant, or if you are breastfeeding. This is because the effects of the study drug on an unborn baby or nursing infant are uncertain. While you are taking afatinib tablets and for at least 28 days after the last dose you will also be asked to use one of the required contraceptive methods (a way to prevent you from becoming pregnant). Your doctor will discuss with you which methods constitute effective contraception.

If you become pregnant, you must tell your study doctor immediately so that he/she may discuss with you the possibility of stopping study treatment. Your doctor will need to report this information and the outcome of your pregnancy to the ETOP safety office.

If you are a man whose partner can get pregnant, you and your partner will need to use birth control during afatinib treatment and for at least 1 month after the last dose. If your partner becomes pregnant while you are receiving study medication, tell your study doctor immediately as they will need to report the outcome of the pregnancy to the ETOP safety office.

BENEFITS

The ultimate goal of conducting clinical research studies in lung cancer patients is to better understand the behaviour of cancer and to find better ways of treatment. We hope that the treatment under this clinical research study will be of benefit to you and/or that it will help others, although we cannot guarantee this.

ALTERNATIVE TREATMENTS

Instead of being in this study, your doctor may recommend that you receive other form of treatment or chemotherapy not given as part of this study.

EXPENSES / REMUNERATION

Afatinib will be provided free of charge by Boehringer Ingelheim

All other expenses, for example, routine standard examinations, will be handled as if you were receiving standard treatment and not participating in the clinical study.

You will receive no payment for taking part in this study.

INSURANCE

ETOP has concluded the appropriate liability insurance for this study (*insert policy number if required according to local guidelines*). Patients, who may suffer injuries due to the study, should report it immediately to their doctor, who will take the necessary steps.

CONFIDENTIALITY

The researchers will need to collect personal information from you such as your age, gender and relevant health information. All information collected is coded in a way that without a key it will not be possible to link the information to your person.

Any personal or health information that is collected will be kept private and confidential. It will be stored securely. Only authorised persons, who understand that it must be kept confidential, will be able to get access to it. In any report of the research made available to the public you will not be referred to by name.

Representatives of the project sponsor, ethics committees or drug regulatory agencies may require access to personal or health information contained in your medical records to verify clinical trial procedures and/or data. Your personal data will be stored in a database and evaluated at ETOP Coordinating Office. ETOP guarantees that the national and international data protection guidelines are respected.

COLLECTION OF BIOLOGICAL MATERIAL

About Using Tissue for Research

In order for you to participate in this study, we need to be sure of the type of lung cancer that you have. Your doctor will be required to send a sample of tumour that was collected either when you were first diagnosed or when you had the relapse to a central laboratory at the *Medical University of Gdańsk, Poland*. The central laboratory performs a pathology review and tests the sample of your tumour for the *HER2* mutation.

In addition, we would like to keep this tissue for future research. If you allow the use of this tissue, it will be kept at the central laboratory at the Medical University of

Gdansk, Poland and used under the responsibility of the Foundation Council of the ETOP.

Your tissue will be very helpful for future research. The research that may be done with your tissue is not designed specifically to benefit you. It may have an impact on the choice of a specific treatment for this type of lung cancer for others. By broadening the knowledge about lung cancer, it might help other patients.

The research will not have an effect on your medical care. We will not examine if cancer is hereditary in your family. In the unlikely case that information relevant to you comes up in the future, we will contact your doctor.

The choice to let us keep the left over tissue for future research is up to you. **No matter what you decide to do, your choice will in no way affect the quality of your care.**

If you decide now to allow ETOP to use your tissue for research, you can change your mind at any time. Just contact your doctor and let him/her know that you do not want ETOP to use your tissue any longer. Then, any tissue that remains will be sent back to the pathologist at your hospital.

The ultimate goals of research using tissue include learning more about what causes lung cancer or other diseases, how to prevent it, and how to treat it.

There are no risks related to research with your tissue. We will make sure that your personal information will be kept private.

TERMINATION OF THE STUDY

You might stop receiving study treatment without your consent for the following reasons:

- a) If your lung cancer worsens or a new tumour develops.
- b) If the doctors treating you detect side effects that they consider dangerous.
- c) If you refuse to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.
- d) If the early analyses of study data show insufficient benefit or a significant potential harm of the treatment.
- e) If the sponsor ETOP decided to stop the study.

NEW INFORMATION ARISING FROM THIS AND OTHER STUDIES

You have the right to be informed of the progress of the research study and of its final results. You have also the right to be informed of all additional results of other studies, which might be important for your treatment or might affect your willingness to continue.

CONTACT PERSONS

The physician in charge of this study is **(give name, telephone number of PI)**. If you need more information about this study before you decide to join, or at any other time, you may wish to contact him/her. In the event that you do decide to participate, he/she should also be called if there are severe side effects from the treatment.

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

TITLE: ETOP 7-14 NICHE

Afatinib in pretreated patients with advanced NSCLC harbouring *HER2* exon 20 mutations

STATEMENT OF PHYSICIAN OBTAINING INFORMED CONSENT

I have fully explained this clinical research study to the patient

In my judgment, and that of the patient, there was sufficient access to information, including risks and benefits, to make an informed decision.

DATE: _____

PHYSICIAN'S SIGNATURE: _____

PHYSICIAN'S NAME: _____

PATIENT'S STATEMENT

I confirm that I have read and understood this Patient Information Sheet dated **dd-mm-yyyy** for the *ETOP 7-14 NICHE* study. I had the opportunity to discuss the clinical study with the undersigning physician, ask questions and I am satisfied with the answers that I have received.

I understand the purposes, procedures and risks of this research project as described in the Information Sheet.

I was informed about alternative treatment options.

I had sufficient time to take the decision.

I take note that a sample of my tumour tissue will be collected, sent to the central laboratory at the Medical University of Gdansk, Poland, and used for the purpose of quality assurance (central pathology review) and review of *HER2* mutation status.

I take note that future cancer research with my biological material will only be done after approval by the relevant ethics committee.

Please choose one:

- I allow the use of my tissue sample for future cancer research.
- I do not allow the use of my tissue sample for future cancer research.

I take note that any research will be such that my privacy will be fully protected

I am informed that an injury as a result of participating in this research project is covered by an insurance.

I agree that my General Practitioner will be informed of my participation in this study

I freely agree to participate in this project according to the conditions in the Patient Information Sheet. I understand that I withdraw my consent any time without giving any reasons and that this will not affect my future medical care.

I understand that my personal data leaves the hospital only in anonymised form and that the researchers will not reveal my identity and personal details if information about clinical study is published. For quality control and inspections I give permission to individuals from ETOP, to staff from the health authorities and ethics committees for to have access to my medical records. In such cases personal information will always remain confidential.

I am aware that the procedures and restrictions described in the Patient Information Sheet have to be followed.

In the interest of my personal health the researcher can take me off the study.

I have received a copy of the Patient Information Sheet and Consent.

DATE: _____ [Date must be written by the patient]

PATIENT'S SIGNATURE: _____

PATIENT'S NAME: _____

PATIENT'S DATE OF BIRTH: _____

Patient ID number assigned at randomization: _____

PLEASE KEEP A COPY OF THE SIGNED INFORMED CONSENT. DO NOT SEND THE SIGNED INFORMED CONSENT FORM TO ETOP.