Clinical trial/research prospectus and consent form

IRB Number：202504068RINB

Please read the content carefully and sign the consent form after the host or his authorized personnel explain it to you.

Project Title:

Explore the primary resistance mechanisms of anaplastic lymphoma kinase inhibitors.

Study Institutions: National Taiwan University Hospital, Departments of Thoracic Surgery, Internal Medicine, and Oncology; National Taiwan University Cancer Center, Departments of Surgical Oncology, General Internal Medicine, and Medical Oncology.	**Sponsor/Pharmaceutical Company:** Taiwan Society of Thoracic Surgeons **Research Funding Source:** Taiwan Society of Thoracic Surgeons

Principal Investigator: Chen Jin-Shing, Director, Department of Surgery, National Taiwan University Hospital

Co-Investigator: Hsu Hsao-Hsun, Director, Department of Medical Oncology, National Taiwan University Cancer Center

Co-Investigator: Huang Pei-Ming, Director, Department of Thoracic Surgery, National Taiwan University Hospital

Co-Investigator: Wu Shang-Gin, Attending Physician, Department of Chest Medicine, National Taiwan University Hospital

Co-Investigator: Yang Chih-Hsin, Superintendent, National Taiwan University Cancer Center

Co-Investigator: Shih Chin-Yuan, Director, Department of Chest Medicine, National Taiwan University Hospital

Co-Investigator: Ho Chao-Chi, Associate Director, Department of Internal Medicine, National Taiwan University Hospital

Co-Investigator: Tsai Tung-Ming, Attending Physician, Department of Surgical Oncology, National Taiwan University Cancer Center

Co-Investigator: Chen Pei-Hsing, Attending Physician, Department of Thoracic Surgery, National Taiwan University Hospital

Co-Investigator: Lin Yen-Ting, Attending Physician, Department of Chest Medicine, National Taiwan University Hospital

Co-Investigator: Liao Pin-Chih, Attending Physician, Department of Oncology, National Taiwan University Hospital

Co-Investigator: Huang Yen-Lin, Attending Physician, Department of Pathology, National Taiwan University Hospital

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Co-Investigator: Hsu Chia-Lang, Associate Research Fellow, Department of Medical Research, National Taiwan University Hospital

Contact Person: Dr. Shang-Gin Wu (National Taiwan University Hospital and National Taiwan University Cancer Center) Phone: (02) 23562905, 0972-651242

Subject Name: **Medical Record Number:**

You are invited to participate in this clinical trial/research. This form provides you with relevant information about this trial/research. The principal investigator or authorized personnel will explain the trial/research content to you and answer any questions you may have. Please do not sign this consent form until all your questions have been satisfactorily answered. You are not required to decide immediately whether to participate in this trial/research. Please consider carefully before signing. You must sign the consent form before you can participate in this trial/research. If you agree to participate in this trial/research, this document will serve as your record of consent. Even after you consent, you may withdraw from this trial/research at any time without giving a reason.

(1) Trial/Research Purpose:

In this observational study, we plan to explore the incidence and mechanisms of primary ALK TKI resistance in ALK-positive advanced non-small cell lung cancer patients who develop primary resistance or rapid progression (within 3-6 months) during ALK inhibitor treatment, by re-obtaining tumor specimens for genetic analysis.

(2) Trial/Research Purpose:

In this observational study, we plan to explore the incidence and mechanisms of primary ALK TKI resistance in ALK-positive advanced non-small cell lung cancer patients who develop primary resistance or rapid progression (within 3-6 months) during ALK inhibitor treatment, by re-obtaining tumor specimens for genetic analysis.

Research Background or Current Status of Drugs/Medical Technologies/Medical Devices:

Anaplastic lymphoma kinase (ALK) gene translocation is a known oncogenic driver in non-small cell lung cancer (NSCLC). ALK tyrosine kinase inhibitors (TKIs) have been clearly shown to produce excellent therapeutic effects and prolong survival in patients with this gene mutation. According to current treatment guidelines, ALK inhibitors are the

first-line treatment of choice for ALK-positive advanced NSCLC patients. However, although ALK TKIs are very effective, a small subset of patients do not achieve good therapeutic results, developing resistance and tumor enlargement within 3-6 months of initiating ALK TKI treatment. This is referred to as primary resistance. Currently, many different resistance mechanisms are known, some still ALK-related, and some involving ALK-independent alternative survival pathways. However, most studies focus on acquired resistance, with very few studies on primary resistance, only a limited number of case reports. Therefore, this study aims to investigate the incidence and mechanisms of primary ALK TKI resistance.

This study does not involve drugs or interventional medical technologies/devices.

(3) Trial/Research Inclusion and Exclusion Criteria:

The personnel responsible for this study will evaluate you and discuss the necessary conditions for your participation in this study. You must sign this participant information and consent form before entering the study. Please cooperate by truthfully informing us of your past health conditions. If you do not meet the conditions for participation in this study, you will not be able to participate in this research project.

This study will collect patients treated with first-line ALK tyrosine kinase inhibitors, but only those who develop primary or rapid (3-6 months) resistance will undergo genetic testing of their specimens. Alternatively, if a patient develops primary resistance or rapid resistance after using ALK tyrosine kinase inhibitors and wishes to undergo re-biopsy of the tumor, they can also sign the consent form to be included in this trial.

Inclusion Criteria:

You must meet all the following conditions to participate in this study:

- Age ≥ 18 years old.
- Histologically or cytologically diagnosed NSCLC.
- Known ALK gene translocation in lung cancer.
- Received first-line ALK tyrosine kinase inhibitor treatment and developed resistance within 3-6 months.

- Must be willing to sign the consent form and comply with the relevant regulations of this research project.

Exclusion Criteria:

If you meet any of the following conditions, you cannot participate in this study:

- Refusal to consent and provide the consent form.
- Patients who have already received other lung cancer drug treatments.
- Patients unable to undergo tumor biopsy or venipuncture.

(4) This Trial/Research Method and Related Procedures:

Because you have been diagnosed with advanced non-small cell lung cancer with ALK gene translocation and will receive first-line anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor treatment, you will be invited to participate in this study. If you develop primary or rapid (3-6 months) resistance after receiving ALK TKI treatment, and your tumor re-enlarges or the disease progresses rapidly, your doctor may arrange for a re-biopsy of your tumor. If you participate in this research project, we will perform comprehensive next-generation sequencing (NGS) and RNA sequencing (RNA-seq) on your re-biopsied tumor tissue sample using Guardant360 TissueNextTM, which simultaneously detects 742 cancer-related genes and 28 fusion genes. At the same time, we will retrospectively obtain your initial lung cancer diagnosis tumor biopsy sample and perform the same tests. By comparing the gene test reports before medication and after resistance, we can understand the resistance mechanism. If you do not have a biopsy sample after resistance, a 20 ml peripheral blood sample can also be collected for comprehensive next-generation sequencing to detect gene mutations. In addition, for research purposes, we will also collect some of your relevant clinical data, including your gender, age, smoking history, tumor stage, review of your pathological report, collection of medical information about your condition, treatment drugs, and evaluation reports of treatment response, as well as a series of imaging follow-ups. The entire study period is approximately 2 years, and we expect to collect 20 patients with primary resistance.

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This study does not involve drugs or interventional medical technologies/devices.

(5) Possible Risks and Their Incidence and Management:

This study involves collecting clinical medical data and residual tissue samples after pathological diagnosis, and does not involve drugs or medical technologies/devices, so it will not cause any adverse reactions clinically. As for liquid biopsy by blood draw, there will be a slight stinging sensation during blood collection, and local bruising may occur; some patients may experience vasovagal syncope due to psychological fear, which can be recovered with a short rest and attention to warmth.

(6) Other Alternative Therapies and Explanations:

This research project only investigates the mechanisms of primary resistance to ALK tyrosine kinase inhibitor treatment you have already received. Therefore, your agreement or disagreement to participate in this study will not change the examinations and treatments you should originally receive. Your physician can still choose the next line of targeted therapy or chemotherapy based on your current condition.

(7) Expected Benefits of the Trial/Research:

Through this study, we will be able to understand the mechanisms of primary resistance to ALK tyrosine kinase inhibitors. This may allow for earlier prediction of clinical patient treatment outcomes and medication choices before future drug treatments.

(8) Contraindications, Restrictions, and Requirements for Participants during the Trial/Research:

There are no contraindications or restrictions on activities for participating in this research project.

(9) Confidentiality of Subject Personal Data:

National Taiwan University Hospital will treat any identifiable records and your personal privacy data as confidential in accordance with the law and will not disclose them publicly. Researchers will use a research code to represent your identity, and this code will not display your name, national identification number, address, or other identifiable information. Your identity will remain confidential if trial/research results are published. You also understand that by signing the consent form, you agree that your original medical

records may be directly monitored by monitors, auditors, the Research Ethics Committee, and regulatory authorities (if the trial is governed by the U.S. Food and Drug Administration, then the regulatory authorities include the U.S. Food and Drug Administration) to ensure that the clinical trial/research process and data comply with relevant laws and regulations. The aforementioned personnel also promise not to violate the confidentiality of your identity. Except for the aforementioned institutions' legal right to inspect, we will carefully maintain your privacy.

(10) Withdrawal and Termination of Trial/Research:

If important new information (i.e., information related to your rights or affecting your willingness to continue participating) becomes available during the trial/research, you will be notified and further explanation will be provided. You will be asked to reconsider whether to continue participating, and you are free to decide without causing any unpleasantness or affecting your future medical care by your physician.

The principal investigator may also terminate the entire trial/research if necessary.

When you withdraw from this trial/research or the investigator determines that you are not suitable to continue participating in this trial/research, the data obtained before your withdrawal will be retained and will not be removed. After withdrawal, you can choose how to handle your previously provided specimens and decide whether to consent to the investigator continuing to collect your data.

1. Regarding the specimens I previously provided:

   □ I agree to continue authorizing the use of my specimens for this trial/research. If the use exceeds the scope of the original written consent, my consent must be obtained again.

   □ I do not agree to continue authorizing the use of my specimens for this trial/research, but to ensure the accuracy of completed examinations, I agree that relevant specimens from the trial/research can be reconfirmed by the laboratory and then destroyed.

   □ I do not agree to continue authorizing the use of my specimens for this

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trial/research. Please destroy my previous trial/research-related specimens after I withdraw.

2. After withdrawal, I allow the investigator to continue collecting my data related to this trial/research, such as obtaining subsequent medical processes and laboratory examination results from my medical records. During the continued data collection period, your privacy and personal data confidentiality will still be maintained.

□ I agree to collect.

□ I do not agree to this trial/research continuing to collect or review my data, but records that can be queried from public databases are not subject to this restriction

(11) Damage Compensation and Insurance:

All trials/research inherently carry risks. To ensure that you are protected in case of adverse reactions causing harm due to participation in the trial/research, please read the following explanation carefully:

If, according to the clinical trial/research plan set forth in this study, harm is caused by an adverse reaction, National Taiwan University Hospital will be responsible for compensation. However, foreseeable adverse reactions described in this consent form will not be compensated.

If an adverse reaction or harm occurs according to the clinical trial/research plan set forth in this study, the hospital is willing to provide professional medical care and medical consultation. You do not need to bear the necessary medical expenses for treating adverse reactions or harm.

Except for the aforementioned two forms of compensation and medical care, this study does not provide other forms of compensation. If you are unwilling to accept such risks, please do not participate in the trial/research.

You will not lose any legal rights by signing this consent form.

This study is not covered by human trial liability insurance.

(12) Preservation, Use, and Re-utilization of Subject Specimens (including their derivatives) and Personal Data

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1. Preservation and Use of Specimens and Residual Specimens

(1) Preservation and Use of Specimens (including their derivatives)

For research purposes, the specimens we collect from you will be used according to this research plan. The specimens will be preserved in Laboratory 716 on the 7th floor of the National Taiwan University Hospital Research Building until their preservation period expires in 2045, at which time we will destroy them in accordance with the law. To protect your personal privacy, we will use a trial/research number to replace your name and relevant personal data to ensure complete confidentiality of your specimens and related data. If you have any concerns about the use of specimens, or if you wish to have your specimens destroyed, please contact us immediately (Contact Person: Dr. Wu Shang-Jun, Phone: 0972651242; Contact Unit: Department of Chest Medicine, National Taiwan University Hospital, Phone: 02-23562905, Address: No. 7, Zhongshan South Road, Taipei City). We will then destroy your specimens. You can also contact the hospital's Research Ethics Committee (Phone: (02)2312-3456 ext. 263155) to assist you in resolving any disputes regarding the use of specimens in research.

(2) Preservation and Re-utilization of Residual Specimens (including their derivatives)

Your biological specimens will be encoded with a unique number and stored under the control of the National Taiwan University Hospital Ethics Committee in Laboratory 716 on the 7th floor of the National Taiwan University Hospital Research Building for a maximum of 20 years.

All new research projects must be reviewed and approved by the National Taiwan University Hospital Research Ethics Committee. If the Research Ethics Committee determines that a new study exceeds the scope of your consent, we will be required to obtain your consent again.

Do you agree to provide residual specimens for future lung cancer research and authorize the National Taiwan University Hospital Research Ethics Committee to review whether your consent needs to be re-obtained:

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□ 1. I do not agree to the preservation of my residual specimens; please destroy them after the trial ends.

□ 2. I agree to the preservation of my residual specimens in a non-de-identified manner. If the use exceeds the scope of the original consent, my consent must be obtained again before my specimens can be used for new research.

(3) Relevant Information on Future Use of Residual Specimens:

Residual specimens may be provided, transferred, or authorized for use by the following personnel:

- Domestic academic research institution researchers authorized by the principal investigator.
- Transferred to foreign academic research institutions.

In such cases, the appropriateness of specimen use will be reviewed by the hospital's Research Ethics Committee to protect your rights.

i. Expected Benefits or Expected Research Results of Residual Specimens:

Since the specific medical research for which your residual specimens will be used is currently unknown, it is not possible to predict the possible research results. Preserving residual specimens usually does not provide direct personal medical benefits or compensation to you, but the specimens you provide may promote medical progress and benefit human health.

ii. Research and Personal Disease-Related Examination Results of Residual Specimens

When your residual specimens are used in future research, we will not notify you of the research results or the test results of the specimens

2. Some Types of Specimens and Residual Specimens

During the trial period, your specimens will be stored in Laboratory 716 on the 7th floor of the National Taiwan University Hospital Research Building. If there are residual specimens, they will be stored in Laboratory 716 on the 7th floor of the

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National Taiwan University Hospital Research Building for a maximum of 20 years.

3. Preservation, Use, and Re-utilization of Data

During the trial/research period, according to the type of project and the content you authorize, we will collect your medical records and pathological data, and use a code to replace your name and relevant personal data. If the aforementioned data is in paper form, it will be stored separately from this consent form in a locked cabinet in the research institution; if stored electronically or filed for statistical analysis, it will be stored in a dedicated computer with a password and appropriate antivirus software. These research data and information will be preserved for 20 years.

If the aforementioned data and information are transmitted abroad for analysis and statistics, you will still receive protection consistent with domestic regulations. The principal investigator and the relevant team will do their best to ensure your personal data is properly protected. After the trial ends, we may use the trial data for future medical research.

4. Tumor Tissue Next Generation Sequencing (NGS) Test Results:

In this study, your trial physician will receive the results of gene tests related to the disease (lung cancer) from the test report. Your physician will discuss the gene test results related to the disease (lung cancer) in this report with you based on your condition and treatment. This report is established for research purposes and is not solely used as a basis for determining future treatment. Research conducted on these specimens may help other patients with NSCLC or similar conditions in the future.

(13) Subject Rights:

1. If you have questions about the nature of the trial/research during the process, have opinions on your rights as a patient, or suspect that you have been harmed by participating in the research, you may contact the Research Ethics Committee for consultation at: (02)2312-3456 ext. 263155.

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2. During the trial/research, any significant findings related to your health or disease that may affect your willingness to continue participating in the clinical trial/research will be promptly provided to you. If you decide to withdraw, your physician will arrange for you to continue receiving medical care. If you decide to continue participating in the trial/research, you may need to sign an updated consent form.
3. To conduct the trial/research, you must receive care from Dr. _____. If you have any questions or conditions now or during the trial/research, please do not hesitate to contact Dr. Shang-Gin Wu in the Department of Chest Medicine, National Taiwan University Hospital (24-hour contact number: 0972651242).
4. This consent form is in duplicate. The principal investigator or authorized personnel has given you one signed copy of the consent form and has fully explained the nature and purpose of this study. Dr. _____ has answered your questions about the research.
5. You are not required to pay any fees to participate in this trial/research.
6. Subsidies for participating in research projects: This study does not provide subsidies.
7. If, within two years after the end of the trial, unexpected and directly safety concerns are found, you will also be notified.

(14) Agreements on Expected Commercial Benefits and Their Application from This Research:

If the results of this project trial/research lead to academic publication, intellectual property, and substantial benefits, National Taiwan University Hospital will use them for medical purposes such as disease diagnosis, prevention, treatment, and research in accordance with the law.

Information obtained from this trial/research may lead to discoveries, inventions, or the development of commercial products. All these rights belong to National Taiwan University Hospital. You and your family will not receive any financial benefit or monetary

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compensation, or own any ownership of the aforementioned inventions, from the research results, inventions, or other discoveries in this information.

(15) Signature:

1. The principal investigator, or co-investigator, or their authorized personnel has thoroughly explained the nature and purpose of the research methods described above in this research project, as well as the possible risks and benefits.
   Principal Investigator/Co-Investigator Signature: _____
   Date: _____ Year ____ Month ____ Day
   Signature of other research personnel involved in the explanation and discussion during the consent process: _____
   Date: _____ Year ____ Month ____ Day

2. After the explanation, I have thoroughly understood the research methods described above and the possible risks and benefits. My questions regarding this trial/research project have also been answered in detail. I agree to accept and voluntarily participate in this study and will keep the signed consent form.
   Subject Signature:
   Date: _____ Year ____ Month ____ Day
   Date of Birth: _____ Year ____ Month ____ Day
   Phone:
   Gender:

   Legal Representative/Person with Consent Authority Signature: _____ Date: _____ Year ____ Month ____ Day

   Relationship with Subject (please circle): Spouse, Father, Mother, Son, Daughter, Other: _____

   Date of Birth: _____ Year ____ Month ____ Day

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Phone:

*For situations under Article 79, Paragraph 1, Proviso of the Medical Care Act or Article 12, Paragraph 1, Proviso of the Human Research Act, the exercise of consent authority shall be handled in accordance with Article 79, Paragraph 2 of the Medical Care Act, Article 5 of the Human Trial Management Regulations, or Article 12, Paragraphs 3 and 4 of the Human Research Act, respectively:

*If the subject is incapacitated (a minor under seven years of age or a person under guardianship), the legal representative shall sign; for a person under guardianship, the guardian shall serve as the legal representative.

*If the subject has limited capacity (a minor aged seven or above, or a person who has received assistance declaration from a court due to mental or other intellectual disabilities that significantly impair their ability to express, receive, or recognize the effect of their expressions), the consent of the person themselves and their legal representative or assistant must be obtained.

*If the subject is not incapacitated or has limited capacity, but is unable to communicate and make effective judgments due to lack of mental capacity, the person with consent authority shall sign. The order of persons with consent authority is as follows:

1. For human trials of new drugs, new medical devices, and new medical technologies (Article 5 of Human Trial Management Regulations): (1) Spouse. (2) Parents. (3) Adult children living together. (4) Grandparents living with the subject. (5) Siblings living with the subject. (6) Other relatives who have lived with the subject for the most recent year.
2. For human research (Article 12 of Human Research Act): (1) Spouse. (2) Adult children. (3) Parents. (4) Siblings. (5) Grandparents. For written consent given by relatives in the preceding paragraph, written consent may be given by one person; if the relatives' intentions are inconsistent, their order shall be determined by the preceding paragraphs. Among persons of the same order in the preceding paragraph, those with closer kinship shall be prioritized, followed by those living together if the kinship is the same, and then the older ones if there are no relatives living together.

Witness Signature: _____

Date: _____ Year ____ Month ____ Day

*If the subject, legal representative, or person with consent authority cannot read, a witness should be present during all discussions regarding subject consent. After confirming that the consent of the subject, legal representative, or person with consent authority is entirely voluntary, the witness shall sign the consent form and indicate the date. Personnel involved in the trial/research may not serve as witnesses.

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*If the person is conscious but unable to sign in person, they may use a fingerprint instead of a signature, but a witness must be present.