



ALINA

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## Main Information

**Primary registry identifying number**

LBCTR2020104622

**Protocol number**

BO40336

**MOH registration number****Study registered at the country of origin**

Yes

**Study registered at the country of origin: Specify****Type of registration**

Prospective

**Type of registration: Justify**

N/A

**Date of registration in national regulatory agency**

12/10/2020

**Primary sponsor**

F. Hoffmann-La Roche Ltd

**Primary sponsor: Country of origin**

Germany

**Date of registration in primary registry**

09/12/2020

**Date of registration in national regulatory agency**

12/10/2020

**Public title**

ALINA

**Acronym**

ALINA

**Scientific title**

A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ADJUVANT ALECTINIB VERSUS ADJUVANT PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB (TUMORS 4 CM) TO STAGE IIIA ANAPLASTIC LYMPHOMA KINASEPOSITIVE NONSMALL CELL LUNG CANCER

**Acronym**

ALINA

**Brief summary of the study: English**

This study will evaluate the efficacy and safety of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage IB (tumors 4 cm) to Stage IIIA, anaplastic lymphoma kinasepositive nonsmall cell lung cancer (NSCLC). Specific objectives and corresponding endpoints for the study are outlined below. The primary and secondary efficacy objectives will be analyzed in the intent-to-treat (ITT) population of randomized patients with resected Stage IB (tumors 4 cm) to Stage IIIA NSCLC and in the subpopulation of patients with resected Stage IIIA

NSCLC. Disease-free survival (DFS) as an endpoint does not distinguish between the location of the first documented recurrence of disease or new primary NSCLC. Descriptive statistics (i.e., frequencies and percentages) will be used to explore the first site of recurrence of disease or new primary NSCLC.

**Brief summary of the study: Arabic**



IB مقارنة مع العلاج الكيميائي القائم على البلاتين في المرضى الذين يعانون من المرحلة alectinib ستقوم هذه الدراسة بتقييم فعالية وسلامة سيتم تحليل أهداف (NSCLC) سرطان الغدد الليمفاوية الكشمي غير الصغرى الخلايا ، IIIA (سم إلى المرحلة المستأصلة بالكامل (أورام الذين خضعوا IIIA NSCLC (سم إلى المرحلة 4) الأورام IB للمرضى من المرحلة (ITT) الفعالية الأولية والثانوية في مجموعة العلاج IIIA . للاستئصال وفي تعداد المرضى المصابين بالمرحلة المستأصلة الأولي الجديد. سيتم استخدام الإحصاء NSCLC كنقطة نهاية لا يميز بين موقع أول موقع موثوق لتكرار للمرض أو (DFS) البقاء بدون مرض الأولي الجديد NSCLC الوصفي (أي التكرارات والنسب المئوية) لاستكشاف الموقع الأول لتكرار مرض أو

## Health conditions/problem studied: Specify

The study population will consist of patients who have undergone complete resection with negative margins (R0) of histologically confirmed Stage IB (tumors equal to or larger than 4 cm) to Stage IIIA NSCLC as per UICC/AJCC, 7th edition. Patients will be randomized to receive either alectinib or platinum-based chemotherapy.

## Interventions: Specify

This study has three parts: 1) Screening 2) Treatment 3) Follow-up

The patient will be randomly placed in one of the following groups:

- One group will receive alectinib, (given as 4 capsules by mouth twice a day for up to 24 months)
- The other group will receive treatment with chemotherapy, given by intravenous (IV) infusion (in the vein), for 4 cycles, with each cycle lasting 21 days. Chemotherapy is the current standard of care for lung cancer. Patients in this group will receive one out of the following treatment options at the discretion of the investigator: Cisplatin plus vinorelbine OR cisplatin plus gemcitabine OR cisplatin plus pemetrexed. Carboplatin may be administered instead of cisplatin in one of the previous combinations if at any time, following the first dose, the patient cannot tolerate cisplatin.

During this study, the patient could have up to 18 visits for treatment administration, safety monitoring, and monitoring of the disease for the first 2 years. Afterward, the patient will be monitored for their disease every 24 weeks during Years 3 to 5, and every year thereafter. If the cancer comes back, the study doctor will follow up with the patient about every 6 months until the study is closed down.

This study will comprise approximately 200 centers in around 30 countries worldwide. Approximately 255 patients will be enrolled into the study

## Key inclusion and exclusion criteria: Inclusion criteria

- Signed Informed Consent Form
  - Age equal to and larger than 18 at time of signing Informed Consent Form
  - Complete resection of histologically confirmed Stage IB (tumor equal to and larger than 4 cm) to Stage IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0 -1) NSCLC as per UICC/AJCC, 7th edition, with negative margins, at 4-12 weeks before enrollment
- Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy. Resection by segmentectomy or wedge resection is not allowed.

N3 disease is not allowed.

- If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred.

Systematic sampling is defined as removal of at least one representative lymph node at specified levels.

Complete mediastinal lymph node dissection (MLND) is preferred. MLND entails resection of all lymph nodes at those same levels.

For patients who have undergone a right thoracotomy, sampling or MLND is required at Levels 4 and 7; for those who have undergone a left thoracotomy, sampling or MLND is required at Levels 5 and/or 6 and 7.

Exceptions will be granted for the following situations:

If patients have documented N2 disease in one level (per the UICC/AJCC staging system, 7th edition), not all levels need to be sampled.

If the preoperative staging imaging results (contrast computed tomography [CT] and positron emission tomography scans) do not suggest evidence of disease in the mediastinum, the patient may be considered eligible even if N2 nodal sampling was not performed per surgeon's decision.

- Documented ALK-positive disease according to an FDA-approved and CE-marked test
- Eligible to receive a platinum-based chemotherapy regimen according to the local labels or guidelines
- Eastern Cooperative Oncology Group (ECOG) Performance Status of Grade 0 or 1
- Adequate hematologic function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:  
Platelet count 100 109/L  
ANC 1500/L  
Hemoglobin 9 g/dL

- Adequate renal function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:  
Serum creatinine 1.5 upper limit of normal (ULN) and  
Creatinine clearance (CrCl) 60 mL/min

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of 1% per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

Examples of contraceptive methods with a failure rate of 1% per year include bilateral tubal ligation, male sterilization contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

Women of childbearing potential must have a negative serum pregnancy test results prior to randomization (maximum of 3 days) and within 10 days of the first dose of study drug. First dose of study drug (alectinib or chemotherapy) must be administered within 7 days from randomization.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that



together result in a failure rate of 1% per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

•Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

**Key inclusion and exclusion criteria: Gender**

Both

**Key inclusion and exclusion criteria: Specify gender**

**Key inclusion and exclusion criteria: Age minimum**

18

**Key inclusion and exclusion criteria: Age maximum**

100

**Key inclusion and exclusion criteria: Exclusion criteria**

•Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy

•Prior adjuvant radiotherapy for NSCLC

Radiotherapy in the neo-adjuvant setting is allowed and must be completed at least 4 weeks prior to initiation of study treatment.

•Prior exposure to systemic chemotherapy

Chemotherapy for early-stage of malignancy with curative intent, provided that the last dose received was more than 5 years prior to enrollment, may be allowed upon approval by the Medical Monitor.

•Prior exposure to ALK inhibitors

•Stage IIIA N2 patients that, in the investigator's opinion, should receive PORT are excluded from the study

PORT is not allowed in the study.

•Known sensitivity to any component of study drug (alectinib or planned chemotherapy) to which the patient may be randomized

This includes, but is not limited to, patients with galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption.

•Malignancies other than NSCLC within 5 years prior to enrollment, except for curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, ductal carcinoma in situ, papillary thyroid cancer, or any cured cancer that is considered to have no impact on DFS or OS for the current NSCLC

•Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status postmajor bowel resection

•Liver disease characterized by any of the following:

ALT and AST 3 ULN

or

Impaired excretory function or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, or bleeding from esophageal varices

or

Active viral or active autoimmune, alcoholic, or other types of acute hepatitis.

Active viral hepatitis B is defined as having positive hepatitis B surface antigen (HBsAg).

Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (hepatitis B core antibody [HBcAb] – HbcAb positive, but negative HBsAg) are eligible only if the HBV DNA test is negative.

Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

•Any exclusion criteria based on local labels or guidelines for chemotherapy

•Patients with symptomatic bradycardia

•History of organ transplant

•Known HIV positivity or AIDS-related illness

•Any clinically significant concomitant disease or condition that could interfere with or for which the treatment might interfere with the conduct of the study or the absorption of oral medications or that would pose an unacceptable risk to the patients in this study, in the opinion of the Principal Investigator

•Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial

**Type of study**

Interventional

**Type of intervention**

Pharmaceutical

**Type of intervention: Specify type**

N/A

**Trial scope**

Other

**Trial scope: Specify scope**

**Study design: Allocation**

Randomized controlled trial

**Study design: Masking**

Open (masking not used)

**Study design: Control**

**Study phase**

Active

3

**Study design: Purpose**

Treatment

**Study design: Specify purpose**

N/A

**Study design: Assignment**

Parallel

**Study design: Specify assignment**

N/A

**IMP has market authorization**

Yes, Worldwide

**IMP has market authorization: Specify**

In November 2017 the FDA approved alectinib for the first-line treatment of patients with ALK-positive metastatic non-small cell lung cancer

**Name of IMP**

Alectinib

**Year of authorization**

2017

**Month of authorization**

11

**Type of IMP**

Others

**Pharmaceutical class**

Alectinib is a potent and selective inhibitor of the enzyme activity of ALK (50% of maximum inhibitory concentration [IC50] = 1.9 nM).

**Therapeutic indication**

Alectinib has been approved in Japan for patients with ALK-positive lung cancer that is advanced, has come back, and/or the tumor cannot be removed by surgery. Alectinib has also been approved in the United States and other countries for patients with ALK-positive lung cancer that has spread to other parts of the body.

**Therapeutic benefit**

Alectinib inhibits mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. Alectinib suppressed ALK auto-phosphorylation in cells and showed selective antitumor activity against cell lines with gene alterations of ALK, such as NSCLC and anaplastic large-cell lymphoma (ALCL) cell lines harboring ALK fusions, and a neuroblastoma cell line harboring amplified ALK. In mouse models of subcutaneously grafted human cancer cell lines with gene alterations of ALK, alectinib also exhibited tumor growth inhibition (TGI) and tumor regression when administered orally once daily. In an NCI-H2228 xenograft model of echinoderm microtubule-associated protein-like 4 (EML4) -ALK-positive NSCLC cells induced tumor regression. The rate of TGI at 20 mg/kg/day was 168%, and the effective dose causing 50% TGI (ED50) was calculated to be 0.46 mg/kg/day. At doses of 6 mg/kg/day and above tumor regression occurred. After administration of alectinib for 11 days, the potent antitumor effect was maintained and tumor re-growth did not occur. Additionally, alectinib showed an enhancement of anti-tumor efficacy with good tolerability in combination with other standard chemotherapeutic agents for NSCLC (cisplatin, paclitaxel, gemcitabine and bevacizumab). Alectinib is efficacious in tumor models expressing an ALK fusion bearing mutations, which are associated with resistance to crizotinib, such as L1196M, G1269A and S1206Y. Alectinib is also effective in mouse NCI-H2228 NSCLC xenografts that are already maximally suppressed by crizotinib. Moreover, compared to crizotinib, alectinib reduced tumor growth and prolonged survival in models of brain metastases

**Study model**

N/A

**Study model: Explain model**

N/A

**Study model: Specify model**

N/A

**Time perspective**

N/A

**Time perspective: Explain time perspective**

N/A

**Time perspective: Specify perspective**

N/A

<b>Target follow-up duration</b>	<b>Target follow-up duration: Unit</b>
<b>Number of groups/cohorts</b>	
<b>Biospecimen retention</b> Samples with DNA**	<b>Biospecimen description</b> The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis: -Samples for PK analysis -Pretreatment tumor tissue sample obtained at screening for determination of ALK status for patient eligibility -Tumor tissue sample obtained at the time of recurrence, if deemed clinically feasible, for exploratory research on biomarkers - Plasma samples for exploratory research on biomarkers -Biomarker plasma and tissue sampling will be in accordance with the IRB/EC-approved
<b>Target sample size</b> 225	<b>Actual enrollment target size</b>
<b>Date of first enrollment: Type</b> Anticipated	<b>Date of first enrollment: Date</b> 29/10/2020
<b>Date of study closure: Type</b> Anticipated	<b>Date of study closure: Date</b> 01/11/2026
<b>Recruitment status</b> Pending	<b>Recruitment status: Specify</b>
<b>Date of completion</b> 01/11/2026	
<b>IPD sharing statement plan</b> Yes	<b>IPD sharing statement description</b> The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location. Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes. Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.
<b>Additional data URL</b>	
<b>Admin comments</b>	
<b>Trial status</b> Approved	



## Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
Eudract Number	2017-004331-37

## Sources of Monetary or Material Support

Name
F. Hoffmann-La Roche Ltd

## Secondary Sponsors

Name
NA

## Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Fadi Nasr	Mickhael Gharios Street, Hazmiyeh, Lebanon	Lebanon	009613126 606	nasrfadi@hotmail.com	Mount Lebanon Hospital
Scientific	Fadi Nasr	Mickhael Gharios Street, Hazmiyeh, Lebanon	Lebanon	009613126 606	nasrfadi@hotmail.com	Mount Lebanon Hospital
Public	Arafat Tfayli	American University of Beirut	Lebanon	009611374 374	at35@aub.edu.lb	American University of Beirut (AUBMC)
Scientific	Arafat Tfayli	American University of Beirut	Lebanon	009611374 374	at35@aub.edu.lb	American University of Beirut (AUBMC)

## Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Mount Lebanon Hospital	Fadi Nasr	Head of Oncology and Hematology Department	Approved
American University of Beirut (AUBMC)	Arafat Tfayli	Board certified in internal medicine, hematology, and medical oncology.	Pending



## Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Mount Lebanon Hospital	01/09/2020	Fadi Nasr	nasrfadi@hotmail.com	009613126606

## Countries of Recruitment

Name
Australia
Austria
Belarus
Bosnia and Herzegovina
China
Denmark
Egypt
France
Germany
Greece
Hungary
Italy
Japan
Kazakhstan
Democratic People Republic of Korea
Latvia
The Former Yugoslav Rep of Macedonia
Poland
Portugal
Romania
Russian Federation



Saudi Arabia
Singapore
South Africa
Spain
Taiwan
Thailand
Turkey
Ukraine
United Kingdom
United States of America
Lebanon

## Health Conditions or Problems Studied

Condition	Code	Keyword
NSCLC	Carcinoma in situ of other specified sites (D09.7)	D09.7

## Interventions

Intervention	Description	Keyword
Alectinib	given as 4 capsules by mouth twice a day for up to 24 months	Intervention
Cisplatin plus vinorelbine	intravenous (IV) infusion (in the vein), for 4 cycles, with each cycle lasting 21 days.	Chemotherapy is the current standard of care for lung cancer
cisplatin plus gemcitabine	intravenous (IV) infusion (in the vein), for 4 cycles, with each cycle lasting 21 days.	Chemotherapy is the current standard of care for lung cancer
cisplatin plus pemetrexed	intravenous (IV) infusion (in the vein), for 4 cycles, with each cycle lasting 21 days.	Chemotherapy is the current standard of care for lung cancer
Carboplatin	may be administered instead of cisplatin in one of the previous combinations if at any time, following the first dose, the patient cannot tolerate cisplatin.	Chemotherapy is the current standard of care for lung cancer





## Primary Outcomes

Name	Time Points	Measure
To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage IB (tumors 4 cm) to Stage IIIA, ALK-positive NSCLC	DFS, defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC as determined by the investigator	integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status or death from any cause, whichever occurs first

## Key Secondary Outcomes

Name	Time Points	Measure
To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage IB (tumors 4 cm) to Stage IIIA, ALK-positive NSCLC	OS, defined as the time from randomization to death from any cause	OS, defined as the time from randomization to death from any cause
To evaluate DFS rates for patients on alectinib arm compared with patients on platinum-based chemotherapy arm	DFS rates at landmark timepoints of 3, 4, and 5 years	DFS rates at landmark timepoints of 3, 4, and 5 years
To evaluate the effects of demographics and baseline prognostic characteristics on duration of DFS for patients on alectinib arm compared with patients on platinum-based chemotherapy arm	Effects of demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., disease stage, smoking history, and ECOG Performance Status) on duration of DFS by subgroup analyses	Effects of demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., disease stage, smoking history, and ECOG Performance Status) on duration of DFS by subgroup analyses
To evaluate the location of the first documented recurrence of disease or new primary NSCLC for patients on alectinib arm compared with patients on platinum-based chemotherapy arm	The location of the first documented recurrence of disease or new primary NSCLC	The location of the first documented recurrence of disease or new primary NSCLC
To evaluate the safety and tolerability of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage IB (tumors 4 cm) to Stage IIIA, ALK-positive NSCLC	Incidence of adverse events, with severity determined through use of NCI CTCAE v5.0 Safety laboratory values Vital signs ECG	Incidence of adverse events, with severity determined through use of NCI CTCAE v5.0 Safety laboratory values Vital signs ECG
To characterize the pharmacokinetics of alectinib and its major metabolite(s) in patients with completely resected Stage IB (tumors 4 cm) to Stage IIIA, ALK-positive NSCLC	Plasma concentrations of alectinib and its major metabolite(s) at specified time points	Plasma concentrations of alectinib and its major metabolite(s) at specified time points



## Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files