AstraZeneca

Non-Interventional Study (NIS) Protocol

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Epidemiological study to describe NSCLC clinical management patterns in Central Eastern Europe and Russia. Lung-EPICLIN

Sponsor:

AstraZeneca
Vavilova Street, 24, block 1
119334 Moscow, Russia
Tel:+74957995699
Fax: +74957995698

The following Amendment(s) and Administrative Changes have been made to this Non-Interventional Study Protocol, since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No.	Date of Amendment
		Addendum for Russia	08.12.2009

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of Administrative Change

SUMMARY OF THE NON-INTERVENTIONAL STUDY PROTOCOL

Epidemiological study to describe NSCLC clinical management patterns in Central Eastern Europe and Russia. Lung-EPICLIN

National Coordinators

Professor Tyulandin Sergey
Russian Cancer Research Center
Department of Clinical Pharmacology and Chemotherapy
Kashirskoye Shosse, 23,
115487, Moscow, Russia
Tel: + 74953249844

Number of patients, sites and Countries (planned) in the study

It is estimated that 500 patients will be entered into the study from all over Russia.

Total planned study period

Estimated first patient in: 1st February 2010

Estimated last patient in: 1st August 2010

Estimated last patient out: 1st August 2011

Estimated database lock: 1 st October 2011

Medicinal product (type, dose, mode of administration) and concomitant medication (if applicable)

This is a purely observational study; therefore patients are not assigned to a particular therapeutic strategy beforehand by a protocol. Treatment will be according to current clinical practice.

Overall Aim for this Non-Interventional Study (NIS)

To provide accurate, reliable information on NSCLC clinical management across Central Eastern European countries and Russia in order to detect unmet medical needs of this disease in terms of:

- Patient and hospital characteristics.
- Diagnostic and treatment approaches: initial and subsequent.
- Follow-up patterns in clinical management.
- Outcomes: symptoms, death, functionality, quality of life.
- Use of resources and burden on patients and health care systems.

Study Objectives

a. Descriptive objectives:

<u>Regarding the patient and the disease</u>

- To describe NSCLC patient characteristics.
    - Demographics.
    - Co-morbidities and relevant medical history.
    - Disease-related habits.

- To describe the disease at baseline.
    - Location, tumour type, stage, extent, mutation of biological markers.
    - Related symptoms.
- To describe patient outcomes.
    - Performance Status/ECOG.
    - Therapy outcomes and related events.
    - Disease progression.
    - Death.
    - Quality of life and functional status.

Regarding clinical management

- To describe hospital characteristics.
    - Size and type.
- To describe the diagnostic patterns of the disease.
    - Tests performed.
    - Patient flow-chart until final diagnosis.
- To describe NSCLC treatment received.
    - Surgery.
    - Radiotherapy.
    - Chemotherapy.
    - Other.
- To describe any other use of health care resources.
    - Emergency visits.
    - Hospital stays.
    - Primary care visits.

- Outpatient therapy.
- Home care.

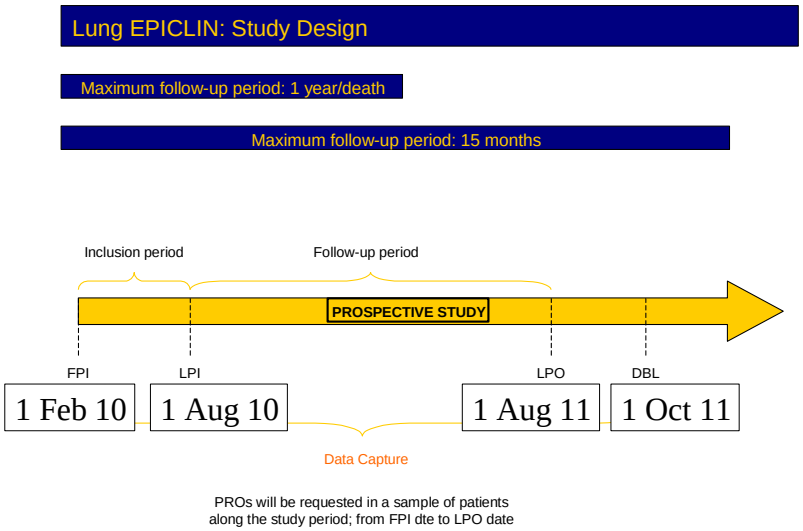
b. Analytical objectives:

- To assess the differences in patient characteristics, disease stage (differentiating between non-advanced disease, locally advanced disease, metastatic disease), and in clinical management across Central Eastern European countries and Russia.
- To detect differences in clinical outcomes and related factors among participating countries.
- To identify factors associated with clinical outcomes (patient, disease stage –see above- and clinical management related factors): predictive modelling for improved patient outcome.
- To identify factors associated with the different levels of functional status and quality of life.
- To compare the use of health care resources among countries.

Study design

Multinational, multicentre, non-interventional, prospective cohort study.

Study Flow-chart



Patient population

All NSCLC patients attending the responsible department of treating this type of patients (e.g. Oncology Department, Pulmonology Department) for the first time (regardless of whether the patient is diagnosed with locally, advanced or metastatic disease) at the participating sites

from the first of January 2010 to the end of July 2010. Patients diagnosed, or even treated, in other departments within the same hospital or in another hospital are susceptible to be included in the study if full access to the patient's medical record is made available.

Methods

The inclusion period will last 6 months, from the 1st of February 2010 to the 1st of August 2010. All patients attending the responsible department of treating this type of patients for the first time during this period should be included in the study. Patients could be retrospectively included in case of not receiving the Ethics Committee approval by the first of January 2010, but only those patients attending for the first time during the enrolment period.

The follow-up period will last for at least one year (the follow-up period will be conducted until the end of July 2011, so the maximum follow-up period will comprise 18 months) or until the patient is deceased, lost to follow-up or changed to another hospital.

Information regarding patients and disease characteristics as well as clinical management approach (diagnostic methods, treatments and follow-up patterns) and final outcomes will be taken from the medical record at each evaluation visit. These visits will be performed according to normal clinical practice.

Functional status and Quality of Life (QoL) questionnaires will be collected directly from the patients immediately after obtaining informed consent.

All patients regardless of whether they are participating in clinical trials or not are eligible to be included in the study. This is a purely observational study, therefore participation in this study will not interfere with participation in a clinical trial.

Statistical Analysis

A descriptive analysis approach will be used to analyse NSCLC population, clinical management, clinical outcomes and use of health care resources.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Non-Interventional Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.4.1)
AZ	AstraZeneca
BSC	Best Supportive Care
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CT-Scan	Computerized Tomography Scan
ECRF	Electronic Case Report Form
ER	Emergency Room
EWB	Emotional well-being
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FACT-L	Functional Assessment of Cancer Therapy - Lung
FNAB	Fine Needle Aspiration Biopsy
FWB	Functional well-being
GCP	Good Clinical Practice
GLM	General Linear Models
ICF	Informed Consent Form
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the investigator co-ordinating the investigators and/or activities internationally
ICU	Intensive Care Unit
NSCLC	Non-Small Cell Lung Cancer
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective
PWB	Physical well-being
PET	Positron Emission Tomography
Principal investigator	A person responsible for the conduct of a clinical study at an investigational

Abbreviation or special term	Explanation
	study site. -Every investigational study site has a principal investigator
PRO	Patient-Reported Outcomes: Umbrella term categorising all types of subjective reported outcomes such as health-related quality of life, treatment satisfaction, subjective health status and subjective symptoms
PS	Performance Status
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
SCLC	Small Cell Lung Cancer
SWB	Social well-being

1. INTRODUCTION

1.1 Background and rationale

Lung cancer is one of the leading causes of death worldwide. Of the 7.3 million deaths caused by cancer every year, 17% are due to Lung Cancer. Prevalence of this disease during 2006 alone in Europe was 386,300 total cases, and 334,800 died during the same period[1].

Of the entire lung cancer population, Non-Small Cell Lung Cancer (NSCLC) is the most common (around 80%) compared with Small Cell Lung Cancer (SCLC)[2]. Squamous Cell Lung Cancer and Adenocarcinoma are the most common subtypes in Europe between 46.5%[3]-33%[4] and 23.6%[3]-30%[4] respectively.

Histopathologically confirmed lung cancer is essential for optimal management of the individual patient and must be secured before chemotherapy and radiotherapy are initiated. However, in rare cases it may be impossible to obtain tumour tissue for examination due to multiple significant co-morbidities or poor performance status. Furthermore, resources available for obtaining correct diagnosis and TNM classification are likely to differ among centres, exemplified by the lack of resources for PET examination in many sites throughout Central Eastern Europe and Russia.

According to national and international guidelines, surgery, chemotherapy and radiotherapy are the cornerstones of NSCLC treatment. Individualized supportive care should constitute an essential element in the management of all patients with NSCLC. Treatment choices are determined by the stage of the disease at each moment and the patient's individual condition (performance status, co-morbidity and age).

The median survival for patients with stage IIIB or IV disease with current first-line chemotherapy regimens is approximately 7-10 months, the one-year survival rate is 35%[5] and response rates range between 17-37%. Once patients experience treatment failure with initial therapy, response to further systemic treatment is approximately 10%[6]. Further progress is anticipated with the novel therapeutic approach of combining existing chemotherapy with drugs that target specific signalling pathways of lung cancer progression.

More than 70% of patients have locally advanced or disseminated disease at diagnosis and are not candidates for localized curative treatment with surgery. High dose radiotherapy can be a curative treatment option in both localized and locally advanced disease. Adjuvant chemotherapy is an option for some of the patients with localized disease and is usually used in combination with radiotherapy in locally advanced NSCLC. These days advanced disease is treated with first line chemotherapy. Recurrent disease can be treated with additional chemotherapy or EGFR inhibitors and/or radiotherapy to symptomatic metastatic spread. Even though these guidelines are officially accepted, it is known, or at least indicated, that there is regional and national variation in the practical management of lung cancer patients throughout all countries in Central Eastern Europe and Russia. This has not been emphasized by the

EUROCARE study which shows variation in lung cancer survival among different countries. It is also known from the Swedish National Registry for lung cancer, for example, that there is even regional variation in treatment and survival. There is also a huge variation in how novel treatments are adopted and implemented among different countries and even among different regions in the same country. When discussing these differences in the management of lung cancer patients, it should be emphasized that we only have limited knowledge of the real magnitude of these national and regional variations.

The treatment of NSCLC metastasis is today more complex and requires dedicated and well educated staff, working in multidisciplinary teams[7-15].

There are several reasons for the variations discussed above such as convenience and cost of treatment, toxicity of chemotherapy (this being the least considered) and also the individual preferences of the physician, all of which might have an impact on the choice of "optimal" treatment.

Consistency of application might not be a problem for the treating oncologist within his or her own practice, but it might have significant ramifications for nursing staff, pharmacists and junior medical staff who are expected to be familiar with and deliver multiple regimens and schedules. The potential for error increases. This can be extrapolated to a larger setting. All European countries are facing common challenges for delivering appropriate, evidence-based care to patients with cancer. Despite tangible improvements in diagnosis and treatment, there are, as discussed above, marked differences in cancer survival throughout Europe. The reliable translation of new research evidence into consistent patient-oriented strategies is a key endeavour to overcome inequalities in healthcare. Clinical-practice guidelines are important tools to improve quality of care by informing professionals and patients about the most appropriate clinical practice[16].

Registries are currently the main source of information on lung cancer, and in fact in clinical trials they are the main tool for making a decision on how to manage the disease. Although they are recognized as useful sources of information, cancer registries, and specifically lung cancer registries, are mainly locally based and maintained in small areas, mostly in reference hospital areas. Most of them do not include broad countrywide information and are therefore only useful at the time of preparing treatment guidelines for hospitals, but not for any decision making as regards the entire Healthcare Systems.

There are country level registries in some European countries, but they do not collect all the data necessary for making the best decision on how to manage the disease in detail and how to implement resources at different levels of the Healthcare System. The same issue with registries occurs worldwide. Most of them, such as those maintained in the United States, Canada or Australia, enjoy a good reputation but have the same lack of information as most of the European registries. The discussion above emphasizes the need for a reliable, accurate and updated multicentre Central Eastern European and Russian cohort study.

A patient-reported outcome (PRO) is the measurement of any aspect of a patient's health status coming directly from the patient, without interpretation of the patient's responses by a physician or anyone else. The use of PRO instruments is part of a general movement toward the idea that the patient, properly queried, is the best source of information about how he or she feels[17].

Patients can indeed understand and report the severity of their symptoms. PROs are currently used in trials that assess the control of cancer symptoms, complementary treatment, and alternative medicine. Patient reporting is also reliable in documenting the severity of specific disease-related patient symptoms, typically by the use of a linear analogue scale. The usefulness of PROs in clinical trials is especially important in the context of modern managed health care and the 15 minute visit, which allows barely enough time to discuss the disease itself, let alone issues about symptoms. Undoubtedly, clinicians support the use of information provided by the patient on their condition as a key component of medical care[19].

The lack of good, updated, organized and accessible local epidemiological data, clinical management data and knowledge of how to use healthcare resources in view of the many different treatment regimens available, all leads to an underestimation of the actual burden of lung cancer and associated unmet medical needs, with consequences for payers and health decision makers, at the national and European level, as well as for patients and society.

Currently, most investigation into lung cancer, and specially NSCLC is focused on the clinical outcomes of some treatment strategies and, in the field of epidemiology, in assessing the likely risk factors associated with the disease. There are only a few current studies on how patients are managed in real life practice[20-24], these are clinical epidemiology studies. In view of this it would be very useful for physicians to be informed of treatment strategies used around Central Eastern Europe and Russia, and also to have information on the impact of these treatment options on overall costs and patient outcomes, in order to determine the best management pattern for each type of patient.

The rising costs of cancer treatments, addressing the needs of reimbursement and payer agencies are all important for gaining regulatory approval for new treatments. Governments and decision makers are struggling to provide access to new therapies against constrained health care budgets. Along with information on clinical efficacy, decision makers would benefit from data on clinical effectiveness and cost-effectiveness. The EPICLIN study is designed to provide information on the clinical effectiveness of existing products, health care resources that are associated with existing therapy and information on patients' quality of life. This is the first study to look at treatment patterns for all lines of treatment across Central Eastern Europe and Russia, identify patterns of care that may be similar or different across Central Eastern Europe and Russia, to make comparisons among treatments and countries and help in to determine effective and cost-effective treatments in the real world.

2. OBJECTIVES OF THE NON-INTERVENTIONAL STUDY

The overall aim of the study is:

To provide accurate and reliable information regarding NSCLC clinical management across Central Eastern European countries and Russia in order to detect unmet medical needs of this disease in terms of:

- Patient and hospital characteristics.
- Diagnostic and treatment approaches: initial and subsequent.
- Follow-up patterns in clinical management.
- Outcomes: symptoms, death, functionality, quality of life.
- Use of resources and burden on patients and health care systems.

2.1 Objectives

2.1.1 Descriptive objectives

Regarding the patient and the disease

- To describe NSCLC patient characteristics.
    - Demographics.
    - Co-morbidities and relevant medical history.
    - Disease-related habits.
- To describe the disease at baseline.
    - Location, tumour type, stage, extent, mutation of biological markers.
    - Related symptoms.
- To describe patient outcome.
    - Performance Status/ECOG.
    - Therapy outcomes and related events.
    - Disease progression.
    - Death.

- Quality of life and functional status.

Regarding clinical management

- To describe hospital characteristics.
  - Size and type.
- To describe the diagnostic patterns of the disease.
  - Tests performed.
  - Patient flow-chart until final diagnosis.
- To describe NSCLC treatment received.
  - Surgery.
  - Radiotherapy.
  - Chemotherapy.
  - Other.
- To describe any other use of health care resources.
  - Emergency visits.
  - Hospital stays.
  - Primary care visits.
  - Outpatient therapy.
  - Home care.

2.1.2 Analytical objectives

- To assess the differences in patient characteristics, disease stage (differentiating between non-advanced disease, locally advanced disease, metastatic disease), and in clinical management across Central Eastern European countries and Russia.
- To detect differences in clinical outcomes and related factors among countries.
- To identify factors associated with clinical outcomes (patient, disease stage –see above- and clinical management related factors): predictive modelling for improved patient outcome.

- To identify factors associated with the different levels of functional status and quality of life.

- To compare the use of health care resources among countries.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a multinational, multicentre, non-interventional, prospective cohort study to be carried out in a representative selection of hospitals in order to assess lung cancer management in countries throughout Central Eastern Europe and Russia. Within the scope of this study, no diagnostic or monitoring procedures in addition to the routine procedure will be applied to the patients.

To ensure a valid picture of real life management, sites will be selected focusing on representative hospitals where lung cancer patients are being managed, in all participating countries.

All NSCLC patients attending the responsible department of treating this type of patients (e.g. Oncology Department, Pulmonology Department) for the first time (regardless of whether the patient is diagnosed with locally, advanced or metastatic disease) at the participating sites from the first of January 2010 to the end of July 2010. Patients diagnosed, or even treated, in other departments within the same hospital or in another hospital are susceptible to be included in the study if full access to the patient's medical record is made available.

Patients could be retrospectively included in case of not receiving the Ethics Committee approval by the first of January 2010, but only those patients attending for the first time during the enrolment period.

Information regarding patient and disease characteristics will be taken from the medical record, as well as management approaches regarding the visit plan, diagnostic tests performed and therapies received by the patient.

A sample of patients will be invited to complete Quality of Life questionnaires when coming to the responsible department of treating this type of patients for assessment. PROs will be collected at each evaluation visit from the first visit (diagnosis) to last visit (after 12 months). PROs will not be completed at treatment administration visits and/or disease- or treatment-related event visits.

The data source for this study will be the medical record at the responsible department of treating this type of patients for each patient. Neither visits nor interventions will be carried out for the study purposes.

The eCRF will be completed at each evaluation visit, entering information on this visit and any other relevant data related to any intermediate visits between the last evaluation visit and the current visit. The study termination module of the eCRF must be completed at the time the investigator is aware of patient's death or withdrawal.

Figure 1 Study flow chart

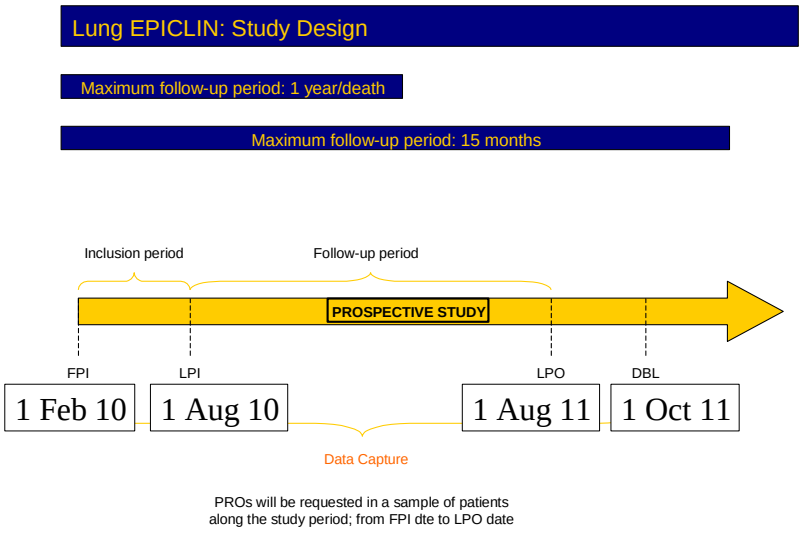

Table 1 Study plan

Time	Inclusion assessment	Each evaluation visit
Informed Consent *(when necessary)*	X	
Patient Demographics	X	
Site information*	X	
Smoking habits	X	
Disease Information	X	X
Diagnosis information	X	
Therapy information	X	X
Clinical outcomes		X
Events due to therapy and/or disease		X
Adverse events due to therapy		X
Use of resources	X	X
Patient Reported Outcomes *(a sample of patients)*	X	X

Time	Inclusion assessment	Each evaluation visit
Study termination *(when investigator is aware)*		X

**At the time of registering a participating site*

3.2 Rationale for Study Design

The EPICLIN study is designed to provide information on the clinical effectiveness of existing products, on health care resources that are associated with existing therapy and on patients' quality of life. This study is the first study to look at the treatment regimens of all lines of treatment across several Central Eastern European countries and Russia to identify patterns of care that may be similar or different across Central Eastern Europe and Russia, to make comparisons among treatments and countries and help to determine effective and cost-effective treatments in the real practice.

The EPICLIN study will provide accurate and reliable scientific information on NSCLC clinical management across Central Eastern Europe and Russia, in order to detect unmet medical needs connected to this disease.

A representative sample of the whole NSCLC population will be involved in order to achieve this objective, therefore sample selection is critical. Avoiding selection bias is essential in this study. Appropriate site selection and the inclusion of all patients attending a specific department responsible of treating this type of patients are also essential requirements.

Moreover, it is very important that the disease management pattern is not modified with respect to that of normal clinical practice. Therefore, no extra visits or extra procedures will be performed for study purposes.

Conducting this study with this design will provide high external validity, not only from a scientific point of view, but also regarding healthcare administration and healthcare providers.

This study will thus help to address a number of issues regarding the burden of NSCLC and the variability of treatment and outcomes throughout Central Eastern Europe and Russia in real practice.

3.3 Selection of patient population

3.3.1 Investigators

Patients will be recruited by clinicians working at the responsible department of treating this type of patients where he/she is being treated for his/her lung cancer. All or some of the investigators of each site could be included.

The number of participating investigators will be that needed to ensure the inclusion of the number of subjects calculated for the sample size.

The selected investigators must be representative of the whole responsible clinicians of treating this type of patients in each country and should not be selected based on any other criteria, in order to avoid any selection bias.

There is no minimum or maximum number of patients per investigator. Each investigator should invite all patients coming to his/her clinic for the first time, to participate in the study, if inclusion/exclusion criteria are met.

3.3.2 Patient population selection criteria

All patients with NSCLC attending participating hospitals during the pre-specified period will be eligible to participate in the study.

Patients will be asked to sign an informed consent form which specifies that there will be no change in clinical management because of the study and that it only involves collecting information[†].

All patients regardless of whether they are participating in clinical trials or not are eligible to be included in the study. This is a purely observational study, therefore participation in this study will not interfere with participation in a clinical trial. The participation in this study will not prevent the patient from being given the opportunity of receiving an investigational product or participating in another study.

A sample of patients (25% of the whole sample) will be asked to complete Quality of Life questionnaires when attending the programmed assessment visits to the physician. Only patients who are not participating in clinical trials will be asked to participate in the Quality of Life sub-study. These patients will be asked to sign a specific informed consent form.

3.3.2.1 Inclusion Criteria

For inclusion in the study, patients must meet all of the following criteria:

1. Confirmed NSCLC diagnosis (e.g. bronchoscopic biopsy or FNAB), all stages, men and women, attending the responsible department of treating this type of patients for the first time between January 1st, 2010 and August 1st, 2010.

2. For PRO sub-sample: ability to read and write since they will be asked to participate in the PRO part of the study. Selection will not be based on the disease stage of each patient, in order to avoid a selection bias.

3. 18 years of age or more.

[†] *Only when required by local authorities.*

3.3.2.2 Exclusion Criteria

According to the study design there will not be any exclusion criteria in order to provide a high external validity and to obtain the most accurate real daily practice information.

3.3.3 Discontinuation of patients from assessment

3.3.3.1 Criteria for Discontinuation

The following criteria for withdrawal only apply to patients who, according to local regulations, need to sign the ICF in order to participate in this study . Thus these criteria apply to all patients included in the PRO sample, and to all patients when the ICF is required for all participating subjects:

1. Voluntary withdrawal by the patient who is free to withdraw from this NIS at any time, without prejudice to further treatment.

2. Severe non-compliance with questionnaire instructions as judged by the investigator and/or AstraZeneca's local coordinator.

3. Inadequate enrolment e.g., the patient does not meet the required inclusion/exclusion criteria for the study.

3.3.3.2 Procedures for discontinuation

Patients who wish to withdraw from the PRO sub-study will be immediately withdrawn but the information from the medical record will continue to be collected[‡].

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Study Variables

4.1.1 Information regarding the patients and their disease

Patient Demographics and any other general patient information: Some of the study variables are considered as risk factors of disease progression and functional status therefore, in order to describe the study population, the following information will be collected:

- Gender.
- Date of birth.
- Ethnicity.
- Smoking habits.

[‡] *When ICF is not required for medical record data collection*

- Co-morbidities

Disease information: All aspects related with the disease.

- Disease stage and TNM classification. Only at first visit.
- Primary tumour location: Only at first visit.
- Histological classification and degree of differentiation. (Only at first visit).
- Extent of the disease.
- Related symptoms.
- Molecular biomarkers. (When available). Just to have information on whether such analyses were performed or not in real clinical practice.

Patient Evolution: All information on how the patient is progressing as regards the disease and on therapy-related factors.

- Performance Status (PS)/ECOG, including at diagnosis.
- Weight loss.
- Progression of disease. To be taken into account if disease progression is based on RECIST criteria and/or any other clinical assessment.
- Treatment response: Non-response, partial response, stable disease and complete response according to RECIST evaluation and/or any other clinical assessment.
- Death: Disease-related or for other reasons.
- Disease-related events: Any event the patient experiences that is related with the NSCLC condition (e.g. hospitalisation, primary care consultation, etc).
- Therapy-related events: Any event related to receiving NSCLC treatment (e.g. adverse events).

4.1.2 Information regarding clinical management

Site description and characteristics: In order to describe the main characteristics of the sites providing health care for NSCLC patients. This variable will be not collected for each patient, but for each site involved in the study. This information will therefore be collected at the time of registering a participating site.

- Type of hospital: Teaching hospital, research centre.

Diagnosis Procedures: This is one of the key factors in NSCLC patient management. These variables will allow us to determine how patients arrive at the department responsible of treating this type of patients, and how they have been managed during the period of time from the occurrence of the first symptom to the first therapy prescribed. Information will therefore be recorded regarding:

- Date of diagnosis.
- Disease-related triggering symptoms at diagnosis (Dyspnoea, Asthenia, Chest Pain, Cough, Dysphagia, Haemoptysis).
- Diagnostic technique(s).
- Date of first consultation about symptoms.
- Biomolecular determinations performed or not.
- Any other test performed for diagnostic purposes.

Therapy information: As with diagnosis, therapy is a key factor in terms of lung cancer patient management. The following variables will be collected to this end:

- Surgery: Performed or not and for explorative and/or resection purposes.
- Chemotherapy: onset date, end date, cycles, drug, best response and related adverse events when applicable. Any drugs involved in clinical research will be recorded as "clinical research drug" and onset date, end date and best response will be also collected.
- Radiotherapy. Onset date, end date, type, best response, and related adverse events.
- Other therapy received. Onset date, end date, type, best response and related adverse events. Also supportive care for anaemia should be included in this group: transfusions, erythropoetin, etc.

Use of health resources: This variable is closely related with the previous two, since diagnosis and therapy cover most of the time the patient is in contact with the professional responsible of treating this patients. All variables described above will be used to describe the use of health resources, and the following will also be collected:

- Date of each visit.
- Type of visit: scheduled (for treatment, clinical assessment or both) or non-scheduled.
- Departments visited until referral to the responsible department of treating this type of patients.

- Tests performed (excluding those reported in the diagnosis).

- Length of hospital stay (if applicable), reason for hospitalisation.

- ICU/ER visits.

- Any other specialist visits.

- Any other disease-related health professional visits.

4.1.3 Patient Reported Outcomes (PROs)

Patient Reported Outcomes play a particular role in this study. They will be measured in a sample (25% of the whole sample) of consenting patients at a limited number of sites per country. The sample will include patients at different stages of the disease during the study period who have received different treatment regimens. It is assumed that there will be a representative sample of advanced stage patients.

Each participating country will endeavour to include patients in the PRO sample bearing in mind that the sample must be representative of the whole study population.

Only patients who are not participating in clinical trials will be asked to participate in the Quality of Life sub-study.

- FACT Questionnaires[19]: These are a series of instruments designed to be sensitive to changes in cancer patients. They contain questions designed to measure SWB and EWB as well as PWB and FWB and are simple to use and score. The FACT-L subscale enables the assessment of disease-related symptoms associated with lung cancer.

- EUROQoL/EQ-5D[25]: This is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

4.2 Screening and demographic measurements

Each site will be responsible for maintaining an updated record of the number of patients who are included or not included in this study. An explanation of why patients were not included must be available.

4.3 Measurement of Outcomes Variables

4.3.1 Administration of Patient-Reported Outcomes (PRO)

The PRO questionnaires are self-administered and the patients will be asked to complete them at each evaluation visit. Evaluation visits are those in which an assessment of a procedure (once the responsible clinician of treating this type of patients has the results of such

procedure, and NOT at the time of the visit performing the procedure), or any other tumour evaluation is made by this person.

Appropriate procedures to minimise bias and enhance compliance will be followed throughout the study. The patient will complete the questionnaires independently, so that the answers reflect the patient's perceptions and views. Optimally, the questionnaires will be completed prior to patient-physician interview, before there are substantial professional encounters with transmission of information, such as disease status. Such information may influence the answers the patients provide on questionnaires. Information to the patients on how to complete the questionnaires is provided in the questionnaires.

It is recommended that, following completion of the questionnaires, the investigators perform the clinical evaluation. Before the patient leaves the clinic, the investigator, once the clinical evaluation is finished, should review the patient questionnaires to avoid any uncompleted responses.

The methods for collecting Patient Reported Outcomes (PRO) data are presented below.

4.4 Safety reporting

Due to the non-interventional character of a Non-Interventional Study, no pro-active safety data collection should take place. Only spontaneously mentioned safety events should be reported as required by the post-marketing pharmacovigilance regulations.

4.4.1 Definitions

The definition of an adverse drug reaction (ADR) is given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The investigator is responsible for ensuring this.

Adverse Drug Reaction (ADR)

An ADR is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

5. DATA MANAGEMENT

5.1 Collection, monitoring and processing of data

An electronic case report form (eCRF) and also a paper case report form (pCRF) will be provided to all participating countries that have been designated to answer all of the proposed variables. Each local study coordinator will be responsible for providing this eCRF/pCRF to each participating site in time for them to start the study on time according to the timelines described in this protocol.

Data will be collected from the medical record of each patient at the time of each evaluation visit. At this time the investigator or the person responsible for recording the data will enter information into the eCRF/pCRF regarding the current visit and any relevant information regarding intermediate visits (from the previous one to the current one) of the patient to the department responsible of treating this type of patients.

Data entered into the eCRF, once saved, will be automatically transferred to the core Data Management Office, where all the information will be tabulated.

Although the source data will not be verified in this study, the eCRF will have a set of data checks in order to avoid inconsistencies. Data will not be monitored in this study, but queries could arise from the person responsible for Data Management.

Furthermore, in order to make data collection easier, the eCRF will provide an instruction manual on how to complete each of the variables, as well as examples for each of them.

There will be NO possibility of adapting or changing data or adding any data to those collected for entry into the eCRF.

The following will be globally organized and managed by the AstraZeneca Lung-EPICLIN Coordination Office:

- Development/adaptation of pCRFs and questionnaires.
- Minimum quality assurance requirements.
- Data management.
- Data analysis as described below.

Each country will decide if data is to be collected by a CRO or by hospital personnel.

The following will be locally organized and managed by the local study coordinator:

- All aspects of local data collection.
- Provide information and support to the investigator(s) on data collection.
- Quality assurance. Ensure that minimum quality requirements described in this protocol are met locally.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

All statistical analysis will be performed by the AstraZeneca Lung-EPICLIN Coordination Office and ALMEDIS CRO by means of the SAS® statistical software system.

The two-sided 95% confidence interval will be obtained for the population estimation of the variables.

A comprehensive Statistical Analysis Plan (SAP) will be prepared before database lock.

6.2 Analysis of outcome variables in relation to objectives and hypotheses

Three groups will be created from baseline evaluation for the purpose of data analysis. The patients will be divided according to the baseline stage of their disease (non-advanced NSCLC patients, locally advanced NSCLC patients and metastatic NSCLC patients). For each of them the following variables will be considered:

- Clinical evolution from baseline to each visit:
    - Changes in number of disease-related symptoms.
    - Changes in the extent of the disease.
- Treatment response from baseline to each visit:
    - Number of patients with complete response to treatment.
    - Number of patients with partial response to treatment.
    - Number of patients with stable disease under treatment.
    - Number of patients with progression of disease after treatment.
    - Progression-free time from the last progression or diagnosis to new progression of disease during the study period. The main analysis of the time to disease progression will be a Cox proportional hazards model to estimate the hazard ratio of progression among the analysis groups, with 95% confidence intervals. This will be a 2-sided test of the hypothesis, with a statistical significance level of 0.05. The assigned treatment will be included as a covariate.
- Treatment-related events.

- Mean number of patients with any treatment related event during the study period.
- Mean number of patients with any serious treatment related event during the study period.

- Mortality.
  - Number of patients with documented death during the study period.
  - Number of patients with a documented death due to NSCLC during the study period.

6.3 Method of statistical analysis

Considering the study objectives, the analysis strategy will be as follows:

A descriptive analysis approach will be used to analyse NSCLC population, clinical management, clinical outcomes and health care resources.

Descriptive statistics will include frequency tables (n, mean, median, standard deviation, minimum and maximum for continuous variables and n, frequency and percentage for categorical values).

The assessment of different associations will be as follows:

Logistic and general linear models (GLM) will be used to assess the association of patient characteristics (including stage of disease, histology, PS, etc) and clinical management (independent variable) with clinical outcome variables (clinical evolution, treatment related events, mortality). The interest will separately focus on the treatment differences between each of them or a group of them used. Model-based point estimates of odds ratios and corresponding 95% confidence intervals will be reported (when applicable). P-values will be reported for comparisons between different treatments.

A descriptive analysis approach will be used to assess factors related with the use of health care resources, and a comparison of the level of use of health care resources will also be made.

The assessment of quality of life will be as follows:

Changes in FACT-L total score from first visit to the visit prior to a specific treatment response with focus on treatment differences. This is a variable of particular interest and will be analysed using an ANCOVA model.

Changes in FACT-L total score from first visit to each assessment will be analysed using an ANCOVA model.

Changes in EQ-5D total score from first visit to the visit prior to a specific treatment response with focus on the differences between treatments. This is a variable of particular interest and will be analysed using an ANCOVA model.

Changes in EQ-5D total score from first visit to each assessment will be analysed using an ANCOVA model.

6.4 Determination of sample size

The most important aspect when selecting sites is their representativeness in each country. If 80% of NSCLC patients are being managed in large teaching hospitals, then 80% of the study sample should come from this type of hospital. Participating sites should include all the patients meeting inclusion/exclusion criteria during the inclusion period assumed to be 25-30 patients in a 6-months period, since there is no seasonal variability. (Estimated number of new lung cancer patients in large hospitals is 100-125/year).

Since the main objective is to obtain reliable information on how patients are being managed, it is essential to obtain valid information on all therapy lines. For this reason, and bearing in mind the high mortality of the disease, it is very important to have access to a sample large enough to finally provide a core group of patients likely to receive advanced treatment lines (including investigational products), and also to allow comparisons.

Assuming that generally in Central Eastern Europe and Russia 80-85%[2] of lung cancers are NSCLC, 80-90% of them are diagnosed at phase IIIb/IV (patients most likely to receive several lines of treatment) and of these 75-80% are treated (approximately 33% with investigational products). No published information is available regarding the proportion of these patients who will achieve further treatment lines, but for sample estimation we assumed that no more than 10% of newly diagnosed NSCLC patients would receive an active third line treatment.

It is estimated that approximately 4,000 patients will be included across several Central eastern European countries and Russia. This amount of patients would enable us to obtain a sample of approximately 400 IIIb/IV treated NSCLC patients throughout Europe.

For the descriptive analysis, 600 NSCLC phase IIIB-IV third line patients will allow us to estimate a proportion of 0.5 (taking into account that this is a novel study in NSCLC and the most pessimistic scenario must be considered) with a precision of 0.04, which means estimating 50% with a confidence interval from 46% to 54% (α=0.05).

It was also considered that the analytical objectives of the study would require multivariate analysis to determine the above sample size. This analysis will consider the main risk variables as independent variables. Based on the formula provided by Freeman[26] (the sample size must be 10 times the number of variables plus one) in order to perform such multivariate analysis, and having as variables for comparison: treatment, cycle, phase, primary tumour location, extent of disease, prior surgery, age, sex, EGFR markers, habits, PS/ECOG and type of hospital, the total sample size of 4,000 patients is advised.

A sample of 25% of patients per country will be included in the Quality of Life descriptive sub-study. Whether a sample from each site in the study is included in the sub-study will depend on the number of sites participating in each country. The number of sites involved will be determined bearing in mind that 25% of the total population included in the study must be invited to participate in the Quality of Life sub-study.

7. STUDY MANAGEMENT

7.1 Monitoring and Quality Control

Before the first patient is recruited into the study, the local AstraZeneca MC representative or delegate will:

- Establish the adequacy of the facilities and the investigator's capability to appropriately select the sample.
- Discuss with the investigator(s) (and other personnel involved in the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Study Agreement between AstraZeneca/delegate and the investigator.

During the study the local MC representative or delegate may implement several activities to assure compliance with AZ standards of quality. These activities could include but are not limited to:

- Contacts with the sites to:
    - Provide information and support to the investigator(s),
    - Confirm that the investigational team is complying with the protocol and data are being accurately recorded in the electronic case report forms (eCRFs).
    - Ensure that the informed consent form is signed and stored at the investigator's site (only if required, see above).
- Monitoring activities for:
    - Checking a sample of ICFs (only if required).
    - Checking that patients exist by reviewing the existence of their medical records (a sample).
    - Different signals (e.g., high rejection rate in a site) should be used as possible triggers for low protocol compliance by investigators. Low rate of NSCLC patients (number of NSCLC identified patients/total number of patients

attending the clinic) in the identification period, compared with the expected prevalence.

If these, or any other signal occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation. These mechanisms should be agreed with the Steering Committee.

In a random sample of sites (10% in each country), a qualified, trained individual other than the Principal Investigator (preferably a CRA) should monitor all the patients included in the study at the selected sites (in terms of ICF collection). This procedure should be performed after 50% of the expected sample is already included.

7.2 Training of staff

The principal investigator will keep a record of all staff members involved in the study (medical, nursing and other staff). He/she will ensure that all staff receive appropriate training relevant to the study, and that any new/relevant information is forwarded to the staff involved.

7.3 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Study Agreement. In the event of any inconsistency between this Study Protocol and the Study Agreement, the Study Protocol shall prevail.

7.4 Study timetable and end of NIS

Before a patient's enrolment in the NIS and any NIS-related procedures are undertaken the following should be fulfilled:

- Signed Study Protocol and other agreements between AstraZeneca and the Principal Investigator / Institution.
- Written approval of the NIS by the Competent Authorities / Leading Ethics Committee (whichever would be appropriate according to local regulations to obtain approval for the NIS).

If AstraZeneca decides to discontinue or terminate the study prematurely, the principal investigator, sub-investigator, the head of the institution, and regulatory authorities must receive written notification of the reasons for the prematurely discontinuation or termination.

The principal investigator/sub-investigator will immediately notify the decision to his / her patients, continue appropriate medical treatment, take necessary measures, and record treatment or measures provided in the source documents.

The planned timetable for the NIS is estimated to be as follows:

Estimated first patient in: 1 st February 2010

Estimated last patient in: 1st August 2010

Estimated last patient out: 1st August 2011

Estimated database lock: 1st October 2011

8. ETHICS

8.1 Ethics review

The final NIS protocol, including the final version of the ICF, must be approved or given a favourable opinion in writing by the Leading Ethics Committee / Competent Authorities (as appropriate according to local regulations).

Ethics Committee should also approve any amendment to the protocol in accordance with local requirements.

8.2 Ethical conduct of the Non-Interventional Study

The NIS will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki 2008 revision, ICH GCPs and the applicable legislation on Non-Interventional Studies.

The Investigator will perform the NIS in accordance with the regulations and guidelines governing medical practice and ethics in the country of the NIS and in accordance with currently acceptable techniques and know-how.

8.3 Informed consent

The information given below refers to any ICF necessary for the performance of this study.

It should be taken into account that some local authorities do no require informed consent for obtaining disease-related data related from medical records which are covered by data protection regulations and the approval of an ethics committee.

Thus a signed ICF from the study population will only be required when the local authorities specifically require it. The procedure for general patients and the PRO sample is described below.

8.3.1 Informed Consent requesting procedures

Informed consent must be given by all patients willing to participate in the study, if required in local regulations.

The principal investigator(s) at each centre will ensure that the patient participating in the study is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to withdraw from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any activities related with the study.

The principal investigator(s) must keep the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

8.4 Patient data protection

This study complies with relevant data protection and privacy legislation. Subjects will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need such information for the purposes of the study.

The Informed Consent Form will incorporate wording explaining that study data on the patient's disease will be stored on a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by an enrolment number / study code specific to each patient making them identifiable.

The Informed Consent Form will also explain that, for the study purposes, authorised representatives of AstraZeneca, a regulatory authority, and an Ethics Committee may require direct access to parts of the hospital or doctors' records that are relevant to the study, including patients medical history.

AstraZeneca may share study data on patients with other companies within its group, with its service providers and its contractors who may only use such data for the purposes described above.

The Sponsoring Company may transfer the patient study data to countries other than the patient's own country for the purposes described in this document. The patient must be made aware that the laws in such countries may not provide the same level of data protection as in his/her country and may not prevent his/her study data from being shared with others. All data that is transferred will be coded.

The results of the study may be published in medical literature, but the patient will not be identified.

If a patient withdraws his / her consent, the Study Investigator will no longer use such patient's study data nor share it with others. AstraZeneca may still use study data that was shared with it before the patient withdrew his / her consent.

8.5 Dissemination of results

Each participating country will be responsible for the local publication strategy although the AstraZeneca Steering Committee should be informed.

A global publication will be prepared focussing on the main comparisons of variables. All external publications (both global and local) will be subject to the AstraZeneca internal review process.

8.6 Publication of results

AstraZeneca is obliged to analyse and report all study data as described in the protocol.

In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. Authors are obliged to preserve the accuracy of the published results. Negative as well as positive results should be published or be otherwise publicly available. AstraZeneca will endeavour to publish the results of the study and undertakes to ensure that the data are reported in a responsible and coherent manner. AstraZeneca will handle the publication of the study results together with the authors; the principal author will take a leading role in this process. AstraZeneca will propose a suitable journal and/or meeting and timelines for publication production for agreement with the authors.

AstraZeneca will co-ordinate the timing and authorship of derived publications or reviews that refer to data from this study to ensure that secondary publications do not jeopardise the primary publication(s) from this project.

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Drug: N/A

Study Code: NIS-ORU-IRE-2009/1

Version : 4.0

Date: 08 December 2009

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

Epidemiological study to describe NSCLC clinical management patterns in Europe. Lung-EPICLIN

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Regional Medical representative

Dr Guy Vandenhoven
Regional Medical R&D Director
AstraZeneca ISMO CEEMEA.
Corporate Village
Da Vincilaan 2 box 2
B-1935 Zaventem
Belgium
+32 2 704.41.61

Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

Epidemiological study to describe NSCLC clinical management patterns in Europe. Lung-EPICLIN

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Marketing Company representative

Professsor Stepanov Alexey
Medical Director
AstraZeneca Russia
Vavilova St., 24, block 1
119334 Moscow Russia

Tel: +74957995699

Date
(Day Month Year)

SIGNATURE OF NATIONAL COORDINATOR

Epidemiological study to describe NSCLC clinical management patterns in Europe. Lung-EPICLIN

I agree to the terms of this protocol of Non-Interventional Study.

Signature

Professor Tyulandin Sergey
Russian Cancer Research Center
Department of Clinical Pharmacology and Chemotherapy
Kashirskoye Sosse, 23,
115487, Moscow, Russia
Tel: + 74953249844

Date
(Day Month Year)

AstraZeneca

Non-Interventional Study (NIS) Protocol – Appendix B

Drug: N/A

Study Code: NIS-ORU-IRE-2009/1

Version : 4.0

Date: 08 December 2009

Appendix B
EQ-5D Questionnaire

Please, insert here your language version of EQ-5D questionnaire

Drug: N/A

Study Code: NIS-ORU-IRE-2009/1

Version : 4.0

Date: 08 December 2009

Appendix C
FACT-L Questionnaire

Please, insert here your language version of FACT-L questionnaire