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Non-Interventional Study(NIS) Report Synopsis	
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Epidemiological study to describe NSCLC clinical management patterns in Central Eastern Europe and Russia. Lung-EPICLIN

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8-P85-1-X Planning, Approval, Conduct and Reporting of Non-Interventional Studies (NISs)

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NIS REPORT SYNOPSIS

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

This NIS report describes study procedures, data management and statistical analysis for the portion of patients recruited in Russian Federation.

Study centre(s)

33 sites in specialized oncology in- and out-patient medical institutions have been included in Russia.

Publications

None

Study Dates

First Patient Enrolled: 01 February 2010
Last Patient Completed: 16 March 2012

Objectives

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.

To collect epidemiological data on EGFR mutation status (M+, M-) in the Russian population

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.

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.

Study design

This was a multinational, multicentre, non-interventional, prospective cohort study 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 were applied to the patients.

To ensure a valid picture of real life management, sites were selected focusing on representative hospitals where lung cancer patients were 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 were included (regardless of whether the patient was diagnosed with locally, advanced or metastatic disease) at the participating sites from the first of February 2010 to the end of July 2010.

Changes to the protocol

Protocol Addendum version 2 issued 08 December 2009 was aimed to introduce the collection of epidemiological data on EGFR mutation status (M+; M-) in Russian population

Protocol Amendment # 1 issued 05 October 2010 extended the enrolment period from 01 August 2010 to 31 March 2011; decreased the observation period from 18 months to 12 months; changed the "Last patient out" date from 11 August 2011 to 31 March 2012; changed the estimated DBL date from 01 October 2011 to 01 June 2012; introduced the Interim Analyses in October 2010; increased the estimated number of enrolled patients from 500 to 800; included two more coordinating investigators: Prof. E. Imyanitov and Prof. V. Moiseenko

Protocol Amendment # 2 issued 05 May 2011 introduced the second interim analyses in June 2011

Protocol Amendment # 3 issued 25 April 2012 was issued to change text of Protocol Addendum; version 2 dated 08 December 2009 to introduce evaluation of distribution of EGFR mutation status (M+; M-; MX) with identification of EGFR mutation type (EGFR Del746-750 and EGFRLeu858Arg) in Russian population

Target patient population and sample size

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

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

The selected investigators had to be representative of the whole responsible clinicians of treating this type of patients in each country and had not to 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 had to invite all patients coming to his/her clinic for the first time, to participate in the study, if inclusion/exclusion criteria were met.

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

Patients had to be asked to sign an informed consent form which specified 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 were participating in clinical trials or not, were eligible for inclusion in the study. This is a purely observational study; therefore participation in this study was not interfering with participation in a clinical trial. The participation in this study was not preventing the patient from being given the opportunity of receiving an investigational product or participating in another study.

The estimated number of patients enrolled in the study in Russian Federation was 500; this number was further increased by Amendment #1 to the Protocol up to 800.

A sample of patients (25% of the whole sample) had to be asked to complete Quality of Life questionnaires when attending the programmed assessment visits to the physician. Only patients who are were participating in clinical trials had to be asked to participate in the Quality of Life sub-study. These patients had to be asked to sign a specific informed consent form.

Inclusion Criteria

For inclusion in the study, patients had to 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 February 1st, 2010 and August 1st, 2010 (by Amendment # 1 extended to 31st, 2012) .
2. For PRO sub-sample: ability to read and write since they had to be asked to participate in the PRO part of the study. Selection had not to be based on the disease stage of each patient, in order to avoid a selection bias.
3. 18 years of age or more.
4. Signed written informed consent (Addendum for Russia)
5. Tumour tissue samples (in paraffin-embedded blocks) suitable for EGFR mutation testing available (Addendum for Russia)

Exclusion Criteria

1. Mixed histology of small cell and non-small cell lung cancer (Addendum for Russia)

Discontinuation criteria

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

1. Voluntary withdrawal by the patient who was 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 did not meet the required inclusion/exclusion criteria for the study.

Patients who wished to withdraw from the PRO sub-study had to be immediately withdrawn but the information from the medical record had to continue to be collected.

Criteria for evaluation (main variables)

Information was taken from the medical records regarding patient and disease characteristics, management approaches regarding the visit plan, diagnostic tests performed and therapies received by the patient. A sample of patients (approximately 25%) was selected to complete QoL questionnaires (Functional Assessment of Cancer Therapy [FACT] and EUROQoL/EURO-QoL-5 Dimensions [EQ-5D]).

Statistical methods

For Continuous data that were assumed to be normally distributed were summarised in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations. Categorical data were summarised in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages

Baseline was defined as Visit 1 data. Last observation carried forward (LOCF) approach was used where applicable.

EGFR mutation status at baseline was summarized by centre and patient. 95% confidence limit for the EGFR mutation positive proportion was calculated using exact test for the binomial proportion.

A stepwise backward selection logistic regression model was used to evaluate the significant factors which may affect the tumour EGFR mutation status (M+/M-). 0.05 level was used as a borderline to stay in the model. The following factors were included into the model: sex, histology type, smoking status, age group, the number of disease symptoms, ethnicity. Odds ratios and 95% confidence limits for the point estimates were reported.

The summary of laboratories performing EGFR mutation tests was provided by centre and EGFR mutation results and by histology group and overall.

The treatment response was summarized by line (disease progression, stable disease, partial response, complete response). Objective response was also presented as a combination of partial and complete response, and it was also summarized by line.

Time to disease progression during the study period was estimated separately for the first and the second line chemo treatment. Adjuvant or other treatment regimens are not included into the analysis. Time to disease progression was estimated as follows:

Time to disease progression (weeks) = (date of disease status evaluation - date of chemo treatment line start)/7.

For the overall analysis the time to disease progression was estimated as the time from the start of the any 'numbered' chemo line (first, second, third and fourth) to the first available disease progression or death after the chemo start. The censoring rules were the same as for the by-line analysis.

A Kaplan-Meier analysis for time to disease progression was performed by line and overall and overall and by EGFR mutation status (M+, M-, overall). Also analysis of time to disease progression was performed for the patients receiving carboplatin doublets and cisplatin doublets for a chemo line. Median time to disease progression was estimated together with 95% confidence intervals. Survival curves were graphically presented for each chemotherapy line

Patient Population

A total of 838 patients were enrolled in the study from 33 sites across Russian Federation. Mean (± standard deviation [SD]) age was 58.7 (±8.5) years, and the majority of patients were male (78.4%).

Results

Demography and baseline characteristics

A total of 838 patients with mean age 58.7±8.5 years were recruited to the study from 33 Russian sites, over three quarters of whom were male, majority of whom were current or ex-smokers.

Overwhelming majority of patients were European (98.0%); only 1.8% of patients were Asian 79.6% patients were Russian, other ethnicities were represented by much lower number of patients. 516 of patients (61.6%) had co-morbidities.

Almost quarter of all patients (25.4%) had metastatic disease (stage IV) at baseline, 63.2% had locally advanced disease (stage III), and 36.7% of patients had early stage disease (stages I and II). Almost two thirds of all patients had some level of lymph node involvement (N1-N3, 63.4%), and approximately quarter had metastasis (M1, 26.1%) Tumor histology showed that squamous cell carcinoma was the most common histology (54.3%), adenocarcinoma constituted 31% plus 6.4% with bronchioloalveolar adenocarcinoma. Tumours were poorly differentiated (G3) or undifferentiated (G4) in almost third these patients .

The most common location of the primary lesion was the upper right lobe (32.8% patients). The NSCLC diagnosis was mostly established using the visualization methods (87.5% cases). Among

visualization methods the leading one was the X-Ray (91.1%) followed by bronchoscopy (81.4% of cases).

EGFR mutation

Biomarkers were assessed for all patients. EGFR mutation was present in 10.1% patients, of whom the majority had adenocarcinoma (58.8%), and 69.4% were female. Most patients having EGFR mutation were less than 70 years old (85.9%) and 71.8% of EGFR positive patients had never smoked. Logistic regression analysis demonstrated that female gender and never having smoked status were significantly associated with EGFR mutations.

The mean turnaround time for EGFR mutation assessment was 2.61±1.81 weeks.

Chemotherapy

Most patients underwent chemotherapy. Platin-containing regimens were mostly administered as first line treatments (cisplatin doublets - 56.5%; carboplatin doublets - 27.0%; other platin-containing regimens - 5.7%).

Treatment outcomes

63.8% patients from those 304 patients with known chemotherapy regimen had progressed during follow-up period after first line therapy; stable disease was observed in 20.1% patients, partial response – in 5.9% patients, complete response – in 10.2% patients.

The median progression free survival after first line treatment was 35.3 weeks.

Quality of Life

QoL was generally poor in the patients completed the questionnaires. Changes in EQ-5D and FACT-L scored were small.

Adverse Events

Overall, 194 AEs were reported at Visit 1 (for 813 patients). For those patients for whom at least 1 AE was reported, median AE number was 2.0. 61 AEs at Visit 1 had CTCAE grade 3 or more, 74 AEs were serious ones.

Treatments

At Visit 1 any surgical procedure was reported for 45.6% patients overall, including tumour resection in 39.1% patients. 18.0% patients underwent radiotherapy at Visit 1 (adjuvant in 10.7% cases and palliative in 7.3% cases). Chemotherapy at Visit 1 was administered to 48.6% patients overall. Use of resources for management of NSCLC patients was high, including diagnostic tests, need for surgery, radiotherapy, chemotherapy and hospitalizations.