NON-INTERVENTIONAL STUDY REPORT SYNOPSIS

An epidemiOlogy study to deteRmine the prevalence of EGFR muTations in RUSsian patients with advanced NSCLC (ORTUS)

Milestones:	Date of first subject in: 02-Sep-2015 Date of last subject in: 04-Apr-2018
Phase of development:	Non-interventional study (NIS)
Sponsor:	AstraZeneca Russia / RUSSCO (Russian Society of Clinical Oncology)

Background/rationale:

Currently there is no precise data concerning the prevalence and types of *EGFR* mutations in cytology samples and in cfDNA before treatment and at the time of progression among Russian patients with advanced NCSLC.

Objectives:

(a) Primary objective

Primary objective of this NIS was to provide accurate and reliable information regarding the EGFR mutations rate tested in cytology and plasma samples before treatment in treatment-naive patients with advanced NSCLC in Russia

Secondary objectives

- To provide accurate and reliable information regarding the *EGFR* mutations profile tested in histology, cytology and plasma samples available at the time of 1st, 2nd and every further progression or after 1.5 year (in case of no progression) after baseline in patients with advanced NSCLC in Russia

- To describe the demographic and clinical characteristics of Russian treatment-naive patients with advanced NSCLC

- To describe treatment approaches in *EGFR*m+ group with advanced NSCLC (1st line, 2nd line and subsequent lines of therapy after every progression)

- To assess progression-free survival time in *EGFR*m+ group (in subgroups on the basis of molecular genetic data and treatment choice)

- To assess routine-practice treatment outcomes/effectiveness (in subgroups on the basis of molecular genetic data and treatment choice)

- To study the association between mutation status assessed based on cytology and plasma samples at baseline and, if possible (depending on the cytology and histology and plasma samples availability) at the time of each progression

Study design:

This was a multicentre, non-interventional, prospective study carried out in representative oncology departments / institutions in order to determine the prevalence of *EGFR* mutations in treatment-naive Russian patients with cytologically verified advanced NSCLC in Russia. No additional procedures besides those already used in the routine clinical practice were applied to the patients. Treatment assignment was performed in accordance to the current practice.

Data source:

EGFR mutations rate before treatment in cytology and plasma samples in treatment-naive patients with advanced NSCLC in Russia was considered as the primary outcome variable in this study.

Along with other diagnosis examinations the analysis of *EGFR* mutations (*EGFR* del746-750, *EGFR* L858R, *EGFR* T790M) in cytology and plasma samples obtained at the Baseline Visit were performed by regional laboratories.

Those patients with *EGFR*m+ NSCLC were observed prospectively during 1.5 years after the baseline visit with regards to NSCLC treatment details and outcomes. *EGFR*m+ patients were also followed up for the molecular genetics monitoring (*EGFR* del746-750, *EGFR* L858R, *EGFR* T790M) at the time of every (the 1st, the 2nd and further) progression or in 1.5 year follow up in case of no progression.

The patients for whom *EGFR* mutations are found participated in the baseline assessments only and were not followed up. Accordingly, one study visit (Screening/Baseline Visit) was planned for all patients and Final Visit in 18 months after baseline assessment was planned for *EGFR*m+ patients. Interim data for *EGFR*m+ patients on the progressions, lines of therapy, collection of cytological, histological and plasma samples at the time of every progression occurrence between Screening/Baseline Visit and Final Visit were also collected throughout the study.

Study population: It was planned to enrol approximately 300 subjects in Russian Federation. Approximately 60 *EGFR*m+ patients were followed for 1.5 years. During the study 423 treatment-naïve patients with advanced NSCLC were screened, and 81 of them were identified to have *EGFR* mutations.

Inclusion criteria: Target study population included treatment-naive patients of both sexes, 18 years and older, with cytologically-verified advanced (stage IIIB-IV) non-squamous, mixed subtypes of NSCLC and NSCLC-NOS, diagnosed before enrolment into the study, consented to participate in this non-interventional study, who visited the oncology hospitals/departments in the Russian Federation.

Exclusion criteria: The exclusion criteria were: squamous NSCLC cytologically confirmed subtype of cancer; patients participating in clinical studies; any medical condition which on the opinion of the investigator may interfere the patient's participation in the study; quality and quantity of the cytological sample material insufficient for the molecular-genetic testing.

Statistical methods: Epidemiological methods mainly were used to represent the study data. A descriptive analysis approach was used to analyse Russian population of patients with advanced NSCLC (including EGFR tests results), clinical management and clinical outcomes.

Results:

Patients subjected to cytological examination on screening

A total of 213 treatment-naïve patients aged 32–86 (mean ± SD: 62.7 ± 9.48 years) with advanced NSCLC were enrolled in this non-interventional study and subjected to the cytological examination on screening. This population included 88 (41.3%) female and 125 (58.7%) male patients; of them, 118 (55.4%) of patients were below 65 years old. The vast majority of patients were Caucasians (n = 211, 99.1%), while only 2 patients were Asians. In accordance to the smoking status the patients could be divided as follows: 98 (46%) of them never smoked, 38 (17.8%) were smoked previously, while 77 (36.2%) were current smokers. The vast majority of patients had IV stage of lung cancer (n = 173; 80.8%), while 40 (18.7%) had IIIB stage. In accordance to the ECOG, nearly half of patients (n = 105; 49.1%) had grade 1, one quarter (n = 53; 24.8%) – grade 0, one fifth (n = 43; 20.1%) – grade 2, while the other patients had grade 3 or 4. In 191 (89.7%; 95% CI: 84.8–93.4%) of 213 patients subjected to the cytological examination on screening no *EGFR*-mutations were found during blood plasma assay. In 15 (7.0%; 95% CI: 4.0–11.3%) and 7 (3.3%; 95% CI: 1.3–6.7%) cases *EGFR* del 746-750 and *EGFR* L858R, correspondingly, were found. Cytological examination revealed higher proportion of *EGFR*-mutations: *EGFR* del 746-750 was detected in 25 (11.7%; 95% CI: 7.7–16.8%) cases, *EGFR* L858R – in 12 (5.6%; 95% CI: 2.9–9.6%) cases, and *EGFR* L861Q – in 1 (0.5%; 95% CI: 0.0–2.6%) case. No mutations were found in 175 (82.2%; 95% CI: 76.3–87.1) patients. The sensitivity for both tests was observed in 16 (42.1%; 95% CI: 26.3–59.2%) patients, while specificity – in 170 (97.1%; 95% CI: 93.5–99.1%) patients. Blood plasma assay gave positive results in 21 cases, while this was confirmed by cytology in 16 cases only.

Negative results of blood test were obtained in 192 patients; of them, in 22 patients the cytology gave a positive result. Thus, the concordance between the assay methods was observed in 186 (87.3%; 95% CI: 82.1–91.5%) patients (κ = 0.48; 95% CI: 0.35–0.60).

EGFR mutations were found in 38 of 213 patients subjected to the cytological examination on screening. All of them were followed for 1.5 years. Premature discontinuation occurred in 30 (78.9%) cases, while only 8 (21.1%) patients completed the 18-month follow-up period. Disease progression was registered in 12 (31.6%) cases. The reasons for premature discontinuation included: loss for follow-up (n = 7; 18.4%), death (n = 12; 31.6%). In 10 (26.3%) patients death occurred due to disease progression. On interim visits (at the time of each progression) no *EGFR* mutations were found in 4 (10.5%) patients, while in 1 (2.6%) patient blood assay revealed *EGFR* L858R, and in 2 (5.3%) patients were found other (e.g. 2) mutations. On final visit only EGFR T790M was found (n = 2; 5.3%).

Among 38 patients with *EGFR* mutations revealed during cytological examination target therapy, chemotherapy, or palliative surgery received 18, 23 and 3 patients correspondingly. In 22 (57.9%) cases the 1 line of therapy was used, while the 2 lines of therapy was used in 5 (13.2%) cases. The most prescribing medications were gefitinib (n = 13; 34.2%), carboplatin (n = 6; 15.8%), etoposide (n = 4; 10.5%), paclitaxel (n = 4; 10.5%), pemetrexed (n = 3; 7.9%), cisplatin (n = 3; 7.9%), and afatinib (n = 2; 5.3%). Therapeutic effects observed on the last completed line of therapy included progression (n = 7; 18.4%), stabilization (n = 8; 21.1%), or partial regression (n = 3; 7.9%). The data on the therapeutic effect were not available in 1 (2.6%) case. The therapeutic effects observed on the line of therapy, which continued at the time of completion of the study, were progression (n = 2; 5.3%), stabilization (n = 6; 15.8%), or partial regression (n = 2; 5.3%). Objective progression was observed in 11 (28.9%) patients, while clinical progression was registered in 9 (23.7%) patients. Gefitinib (1 line treatment) was discontinued more frequently in comparison to other medication; the reasons for discontinuation included disease progression (n = 6; 15.8% of total proportion of discontinued medications) or other reasons (n = 3; 7.9%). Carboplatin or etoposide (1 line treatment) were discontinued due to disease progression in 3 (7.9%) and 2 (5.3%) cases, correspondingly. On the assessment of 15 events in 37 patients the total survival (as mean ± SD) reached 28.15 ± 3.13 months, while the median survival could not be assessed. The number of patients with 1-year survival reached 30 (78.9%); 15 (39.5%) patients deceased during the study. In 13 (34.2) patients death occurred due to NSCLC.

Patients subjected to histological examination on screening

A total of 210 treatment-naïve patients aged 25–85 (mean ± SD: 61.2 ± 9.36 years) with advanced NSCLC were enrolled in this non-interventional study and subjected to the histological screening. This population included 93 (44.3%) female and 117 (55.7%) male patients; of them, 141 (67.1%) of patients were below 65 years old. The vast majority of patients were Caucasians (n = 206, 98.1%), while only 4 patients were Asians. In accordance to the smoking status the patients could be divided as follows: 95 (45.2%) of them never

smoked, 51 (24.3%) were smoked previously, while 64 (30.5%) were current smokers. The vast majority of patients had IV stage of lung cancer (n = 171; 79.9%), while 39 (18.2%) had IIIB stage. In accordance to the ECOG, more than half of patients (n = 127; 59.3%) had grade 1, 36 (16.8%) and 35 (16.4%) patients had grade 0 and grade 2, respectively, while the other patients had grade 3 or 4. In 180 (85.7%; 95% CI: 80.2–90.1%) of 209 patients subjected to the histological examination on screening no *EGFR*-mutations were found during blood plasma assay. In 10 (4.8%; 95% CI: 2.3–8.6%), 2 (1.0%; 95% CI: 0.1–3.4%) and 12 (5.7%; 95% CI: 3.0–9.8%) cases *EGFR* del 746-750, *EGFR* L858R and *EGFR* T790M, correspondingly, were found. Other (e.g. 2 mutations) was stated in 5 (2.4%; 95% CI: 0.8–5.5%) cases. Histological examination revealed higher proportion of *EGFR*-mutations: *EGFR* del 746-750 was detected in 24 (11.4%; 95% CI: 7.5–16.5%) cases, *EGFR* L858R – in 11 (5.2%; 95% CI: 2.6–9.2%) cases, and *EGFR* L861Q – in 1 (0.5%; 95% CI: 0.0–2.6%) case. No mutations were found in 167 (79.5%; 95% CI: 73.4–84.8) patients, while other (e.g. 2 mutations) – in 7 (3.3%; 95% CI: 1.4–6.7%) cases. Both tests were sensitive in 12 (28.6%; 95% CI: 15.7–44.6%) patients, and specific – in 154 (92.2%; 95% CI: 87.1–95.8%) patients. Blood plasma assay gave positive results in 25 cases, while this was confirmed by histology in 12 cases only. Negative results of blood test were obtained in 184 patients; of them, in 30 patients the histology gave a positive result. Thus, the concordance between the assay methods was observed in 166 (79.4%; 95% CI: 73.3–84.7%) patients ($\kappa = 0.24$; 95% CI: 0.12–0.37).

EGFR mutations were found in 43 of 210 patients subjected to the histological examination on screening. All of them were followed for 1.5 years. Premature discontinuation occurred in 27 (62.8%) cases, while 16 (37.2%) patients completed the 18-month follow-up period. Disease progression was registered in 5 (11.6%) cases. The reasons for premature discontinuation included: loss for follow-up (n = 3; 7.0%), death (n = 19; 44.2%). In 14 (32.6%) patients death occurred due to disease progression. On final visit no *EGFR* mutations were found in 3 (7.0%) patients, while in 1 (2.3%) patient blood assay revealed *EGFR* L858R.

Among 43 patients with *EGFR* mutations revealed during histological examination target therapy, chemotherapy, or palliative surgery received 9, 12 and 2 patients correspondingly, while 2 patients received combined therapy. In 32 (74.4%) cases the 1 line of therapy was used, while the 2 lines of therapy were used in 2 (4.7%) cases. The most prescribing medications were gefitinib (n = 8; 18.6%), carboplatin (n = 4; 9.3%), paclitaxel (n = 4; 9.3%), bevacizumab (n = 3; 7.0%), etoposide (n = 2; 4.7%), and cisplatin (n = 2; 4.7%). Therapeutic effects observed on the last completed line of therapy included progression (n = 11; 25.6%), stabilization (n = 7; 16.3%), or partial regression (n = 5; 11.6%). The data on the therapeutic effect were not available in 2 (4.7%) cases. The therapeutic effects observed on the line of therapy, which continued at the time of completion of the study, were full regression (n = 2; 4.7%), progression (n = 1; 2.3%), stabilization (n = 3; 7.0%), or partial regression (n = 1; 2.3%); no data were available in 1 (2.3%) case. Objective progression was observed in 5 (11.6%) patients, while clinical progression was registered in 3 (7.0%) patients. Gefitinib (1 line treatment) was discontinued more frequently in comparison to other medication; the reasons for discontinuation included disease progression (n = 4; 9.3% of total proportion of discontinued

medications) or other reasons (n = 2; 4.7%). On the assessment of 22 events in 43 patients the total survival (as mean ± SD) reached 15.02 ± 1.33 months, while the median survival reached 17 months. The number of patients with 1-year survival reached 28 (65.1%); 22 (51.2%) patients deceased during the study. In 17 (39.5) patients death occurred due to NSCLC.

Conclusion:

This large-scale prospective non-interventional study was conducted to receive information about percentage and characteristics of *EGFR*m+ NSCLC patients to provide accurate and reliable information regarding the *EGFR* mutations rate tested in cytology and plasma samples before treatment in treatment-naive patients with advanced NSCLC in Russia. During the study 423 treatment-naïve patients with advanced NSCLC were screened, and 81 of them were identified to have *EGFR* mutations. Nearly half of them were detected during cytological examination, while the others – during histological examination.

In 191 (89.7%; 95% CI: 84.8–93.4%) of 213 patients subjected to the cytological examination on screening no *EGFR*-mutations were found during blood plasma assay. In 15 (7.0%; 95% CI: 4.0–11.3%) and 7 (3.3%; 95% CI: 1.3–6.7%) cases *EGFR* del 746-750 and *EGFR* L858R, correspondingly, were found. Cytological examination revealed higher proportion of *EGFR*-mutations: *EGFR* del 746-750 was detected in 25 (11.7%; 95% CI: 7.7–16.8%) cases, *EGFR* L858R – in 12 (5.6%; 95% CI: 2.9–9.6%) cases, and *EGFR* L861Q – in 1 (0.5%; 95% CI: 0.0–2.6%) case. No mutations were found in 175 (82.2%; 95% CI: 76.3–87.1) patients. The sensitivity for both tests was observed in 16 (42.1%; 95% CI: 26.3–59.2%) patients, while specificity – in 170 (97.1%; 95% CI: 93.5–99.1%) patients. Blood plasma assay gave positive results in 21 cases, while this was confirmed by cytology in 16 cases only. Negative results of blood test were obtained in 192 patients; of them, in 22 patients the cytology gave a positive result. Thus, the concordance between the assay methods was observed in 186 (87.3%; 95% CI: 82.1–91.5%) patients ($\kappa = 0.48$; 95% CI: 0.35–0.60).

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higher proportion of *EGFR*-mutations: *EGFR* del 746-750 was detected in 24 (11.4%; 95% CI: 7.5–16.5%) cases, *EGFR* L858R – in 11 (5.2%; 95% CI: 2.6–9.2%) cases, and *EGFR* L861Q – in 1 (0.5%; 95% CI: 0.0–2.6%) case. No mutations were found in 167 (79.5%; 95% CI: 73.4–84.8) patients, while other (e.g. 2 mutations) – in 7 (3.3%; 95% CI: 1.4–6.7%) cases. Both tests were sensitive in 12 (28.6%; 95% CI: 15.7–44.6%) patients, and specific – in 154 (92.2%; 95% CI: 87.1–95.8%) patients. Blood plasma assay gave positive results in 25 cases, while this was confirmed by histology in 12 cases only. Negative results of blood test were obtained in 184 patients; of them, in 30 patients the histology gave a positive result. Thus, the concordance between the assay methods was observed in 166 (79.4%; 95% CI: 73.3–84.7%) patients (κ = 0.24; 95% CI: 0.12–0.37).

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Results of this non-interventional study showed that analysis of frequent mutations in the *EGFR* genes performed in routine practice can be insufficient for precise diagnostics of NSCLC, as blood testing for frequent *EGFR* mutations allowed to observe mutations in *EGFR* genes less frequently than in case of histological or cytological examination. It is necessary to discuss possible changes in practical recommendations of NSCLC management in Russia in order to include more accurate and modern methods of genetic analysis (i.e. PCR diagnostics or the complete sequencing of the *EGFR* genes) to implement personalized gene-targeted treatment of NSCLC patients in Russian routine clinical practice.

Publications: No publications were based on this study.

Not applicable.