Lung Cancer 113 (2017) 37–44

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

EGFR mutation prevalence in Asia-Pacific and Russian patients with advanced NSCLC of adenocarcinoma and non-adenocarcinoma histology: The IGNITE study

Baohui Han[a,*], Sergei Tjulandin[b], Koichi Hagiwara[c], Nicola Normanno[d], Laksmi Wulandari[e], Konstantin Laktionov[f], Achmad Hudoyo[g], Yong He[h], Yi-Ping Zhang[i], Meng-Zhao Wang[j], Chien Ying Liu[k], Marianne Ratcliffe[l], Rose McCormack[l], Martin Reck[m]

[a] *Department of Respiratory Medicine, Shanghai Chest Hospital, Jiao Tong University, 241 Huaihai West Road, Shanghai, 200030, China*
[b] *Department of Clinical Pharmacology and Chemotherapy, N. N. Blokhin Russian Cancer Research Center, 24 Kashirskoye Shosse, Moscow, 115478, Russia*
[c] *Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi, 329-0498, Japan*
[d] *Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori "Fondazione Giovanni Pascale", IRCCS, Via Mariano Semmola, Napoli, 80131, Italy*
[e] *Department of Pulmonology, Dr Soetomo General Hospital, No. 6-8 Surabaya, Jawa Timur, 60285, Indonesia*
[f] *Department of Clinical Biotechnology, N. N. Blokhin Russian Cancer Research Center, 24 Kashirskoye Shosse, Moscow, 115478, Russia*
[g] *Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Indonesia – Persahabatan Hospital, 2nd Floor Jl. Persahabatan Raya No. 1, Rawamangun, Jakarta, 13230, Indonesia*
[h] *Department of Respiratory Medicine, Daping Hospital, The Third Military Medical University, No.10 Daping Changjiang Branch Road, Chongqing, 400042, China*
[i] *Department of Chemotherapy, Zhejiang Cancer Hospital and Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, 38 Guangji Road, Hangzhou, Zhejiang, 10022, China*
[j] *Department of Respiratory Medicine, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 1 Shuaifuyuan Street, Dongcheng District, Beijing, 100730, China*
[k] *Division of Thoracic Medicine, Chang Gung Memorial Hospital, Chang Gung University, 199 Tung Hwa North Road, Taipei, 105, Taiwan*
[l] *AstraZeneca, Mereside, Alderley Park, Macclesfield, SK10 4TG, United Kingdom*
[m] *Department of Thoracic Oncology, LungenClinic Grosshansdorf, Airway Research Center North (ARCN), Member of the German Centre for Lung Research (DZL), Wöhrendamm 80, Grosshansdorf, 22927, Germany*

ARTICLE INFO

Keywords:
Adenocarcinoma
Circulating free tumour-derived DNA
Diagnostic
Epidermal growth factor receptor
Non-small-cell lung cancer

ABSTRACT

Objectives: Limited understanding exists of epidermal growth factor receptor (*EGFR*) mutation frequency in less common subgroups of advanced non-small-cell lung cancer (aNSCLC) (e.g. squamous cell carcinoma [SCC]), and to what extent local practices exclude patients from *EGFR* testing based on their clinical characteristics.
Materials and methods: IGNITE (non-comparative/-interventional; NCT01788163) was conducted in 90 centres (Asia-Pacific/Russia). Eligible patients: local/metastatic aNSCLC; chemotherapy-naïve, newly-diagnosed/recurrent disease after resection; ineligible for curative treatment. Patients provided a tissue/cytology (all) and a blood plasma (China/Russia/South Korea/Taiwan) sample. Primary endpoint: *EGFR* mutation frequency in aNSCLC patients (adenocarcinoma [ADC]/non-ADC), as per local practices.
Results: 3382 patients were enrolled. *EGFR* mutation frequencies for evaluable tissue/cytology samples in Asia-Pacific and Russian patients: 49.3% (862/1749) and 18.0% (90/500) for ADC tumours; 14.1% (74/525) and 3.7% (15/402) for non-ADC; 9.9% (40/403) and 3.7% (13/349) for SCC. Of Russian patients with SCC tumours harbouring common, activating *EGFR* mutations, 6/9 were never-/former-smokers. Mutation status concordance between 2581 matched tissue/cytology and plasma samples: 80.5% (sensitivity 46.9%, specificity 95.6%).
Conclusion: EGFR mutation testing should be considered in all Asian aNSCLC patients. Also, as activating *EGFR* mutations were observed in a small number of Caucasian squamous NSCLC patients, testing here may be appropriate, particularly in those with no/remote smoking history. Circulating free tumour-derived DNA is feasible for mutation analysis employing well-validated and sensitive methods, when tumour samples are unavailable.

Abbreviations: ADC, adenocarcinoma; aNSCLC, advanced non-small-cell lung cancer; ASR, age-standardised rate; ctDNA, circulating free tumour-derived DNA; EGFR, epidermal growth factor receptor; LNA, locked nucleic acid; NE, neuroendocrine; NSCC, non-small-cell carcinoma; NSCLC, non-small-cell lung cancer; NPV, negative predictive value; PCR, polymerase chain reaction; PNA, peptide nucleic acid; PPV, positive predictive value; SCC, squamous cell carcinoma; SCCA, small-cell carcinoma; TKI, tyrosine kinase inhibitor; TTF-1, thyroid transcription factor 1; WHO, World Health Organization

* Corresponding author.
E-mail addresses: xkyyhan@gmail.com, hanxkyy@aliyun.com (B. Han).

http://dx.doi.org/10.1016/j.lungcan.2017.08.021
Received 22 June 2017; Received in revised form 25 August 2017; Accepted 28 August 2017

1. Introduction

Statistics indicate that, in Asia, lung cancer is the most common cancer in men (age-standardised rate [ASR; per 100,000] 35.2) and the third most common cancer in women (ASR 12.7) [1]. Similarly, in Russia, lung cancer is the most common cancer in men (ASR 51.4) and the eighth most common cancer in women (ASR 6.8) [1].

Adenocarcinoma (ADC) is among the most common histological subtypes of non-small-cell lung cancer (NSCLC) [2]. NSCLC of ADC histology is reported to be associated with mutations in the epidermal growth factor receptor (*EGFR*) gene in approximately 14–19% of Western patients and 40–48% of Asian patients (corresponding data for non-ADC: 3% and 8%, respectively) [3,4]. Data for Russia specifically have indicated that *EGFR* mutations may occur in 13–20% of Russian patients with NSCLC of ADC histology [5,6].

EGFR tyrosine kinase inhibitors (TKIs) specifically target the protein encoded by the *EGFR* oncogene [7,8], and it is now accepted that response to EGFR TKIs is mainly limited to patients with tumours harbouring activating, targetable, *EGFR* mutations (most common: exon 19 deletion or L858R mutation) compared with wild-type *EGFR* [9]. Furthermore, EGFR TKIs have demonstrated superior efficacy to doublet-chemotherapy in patients with *EGFR* mutation-positive advanced NSCLC (aNSCLC) [10–15].

Current clinical guidelines (National Comprehensive Cancer Network, National Institute for Health and Care Excellence) [16–18] and several working groups [19,20] now advocate mutation testing of tumour samples from patients with non-squamous aNSCLC (and in specific patients with squamous NSCLC [e.g. never-smokers]; European Society for Medical Oncology guidelines) [21] to confirm their suitability for EGFR TKI treatment. Prior to the association with *EGFR* mutation-positive status and response to EGFR TKIs, certain clinical characteristics associated with a high frequency of activating, sensitising *EGFR* mutations (female gender, Asian ethnicity, never-smokers, and ADC histology [3,22]) drove patient selection for mutation testing [23]. However, it is now acknowledged that *EGFR* mutations may occur in any patient [24,25]. Indeed, the number of facilities that conduct mutation testing has risen, reflecting increased clinician demand [26,27].

As the availability of testing becomes more widespread, understanding of the frequency of *EGFR* mutations (particularly in groups that have not previously been widely tested) needs to be updated. Moreover, it is important to assess real-world diagnostic practices to identify areas for improvement, as the methodologies used are highly diverse [16–18,21,26,28], with differences in tumour sampling and *EGFR* mutation testing methodologies not well-documented. Optimum testing methodologies for alternative sample types are, therefore, under investigation, such as circulating free tumour-derived DNA (ctDNA) obtained from blood serum or plasma [4,10,29,30]. Overall, this knowledge will help to ensure that as many patients as possible have access to mutation testing and are treated appropriately based on the molecular characteristics of their disease.

1.1. Objectives

The large, multinational, diagnostic, non-comparative, non-interventional IGNITE study (NCT01788163) assessed *EGFR* mutation frequency in patients with aNSCLC of ADC or non-ADC histologies in a real-world diagnostic setting.

2. Methods

2.1. Study design and patients

Eligible patients (aged ≥18 years) had newly diagnosed, locally advanced (not eligible for curative treatment)/metastatic treatment-naïve NSCLC, or had recurrent disease and surgical resection with/without adjuvant chemotherapy. Provision of a diagnostic tissue/cytology sample was mandatory upon inclusion for all patients, and provision of a routine blood (plasma) sample was mandatory for patients from China, Russia, South Korea, and Taiwan only (other countries included were Australia, Indonesia, Malaysia, Singapore, and Thailand).

The primary endpoint of IGNITE was *EGFR* mutation frequency in patients with aNSCLC of ADC and non-ADC histologies. Secondary endpoints included: *EGFR* mutation testing practices; level of concordance in *EGFR* mutation status between matched tissue/cytology and blood (plasma) samples; correlations between *EGFR* mutation status and demographic data/disease status; and treatment decisions following *EGFR* mutation testing (not reported).

All patients provided written, informed consent. Study approval was obtained from independent ethics committees at each institution. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements for non-interventional studies, and AstraZeneca's policy on bioethics and human biological samples.

2.2. Procedures

EGFR mutation testing and results data for tumour samples obtained prior to enrolment in IGNITE were used where available. For tests conducted in IGNITE, diagnostic tissue/cytology samples underwent *EGFR* mutation testing as per local practices, following histopathologic review (World Health Organization [WHO] classification) to ensure that samples were adequate for use. Plasma samples were obtained from patients from China, Russia, South Korea, and Taiwan only, as countries deemed most likely to provide sufficient plasma samples to support the concordance analysis: these patients provided 10-mL blood samples, which were processed to plasma, frozen and transported to designated laboratories for testing. In all countries, academic, hospital, or commercial laboratories were utilised for tissue/cytology-based testing; central/regional expert laboratories were utilised for blood (plasma)-based testing.

2.3. Outcomes

Testing methodologies, sample types and availability, and testing turnaround time/success rate/mutation detection rate were captured to assess *EGFR* mutation testing practices. *EGFR* mutation frequency (primary endpoint) was assessed overall, by ADC and non-ADC histologies, and by country/region. *EGFR* mutation concordance between matched tissue/cytology and plasma samples was assessed via: concordance rate; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV); and exact two-sided 95% confidence interval.

2.4. Statistical analyses

EGFR mutation testing practices (enrolled population) and *EGFR* mutation frequency (evaluable tumour [tissue/cytology]/plasma populations) were summarised using appropriate descriptive statistics. It