

Non-small cell lung cancer (NSCLC) driven by activating mutations in epidermal growth factor receptor (EGFR) constitutes up to 10% of NSCLC cases. According to the NCCN recommendations, all patients (with the exception of smoking patients with squamous cell lung cancer) should be screened for the presence of activating EGFR mutations, i.e. deletion in exon 19 or point mutation L858R in exon 21, in order to select the group that benefits from EGFR tyrosine kinase inhibitors (EGFR TKIs) treatment. Among approved agents there are the 1st generation reversible EGFR TKIs, erlotinib and gefitinib, and the 2nd generation irreversible EGFR TKI, afatinib. The objective response rates to these drugs in randomised clinical trials were in the range of 56–74%, and median time to progression 9–13 months. The most common determinant of resistance to these drugs is the clonal expansion of cancer cells with T790M mutation (Thr790Met) in exon 20 of EGFR. Osimertinib (Tagrisso™), a 3rd generation, irreversible EGFR tyrosine kinase inhibitor, constitutes a novel, highly efficacious treatment for NSCLC patients progressing on EGFR TKIs with T790M mutation confirmed as the resistance mechanism. Resistance mutation can be determined in tissue or liquid biopsy obtained after progression on EGFR TKIs. Osimertinib has a favourable toxicity profile, with mild rash and diarrhoea being the most common. In this article, we present three cases that were successfully treated with osimertinib after progression on 1st and 2nd generation EGFR TKIs.

Key words: lung cancer, chemotherapy, TKI inhibitors, osimertinib.

Contemp Oncol (Pozn) 2017; 21 (3): 254–258
DOI: <https://doi.org/10.5114/wo.2017.70116>

Osimertinib – effective treatment of NSCLC with activating *EGFR* mutations after progression on EGFR tyrosine kinase inhibitors

Marcin Skrzypski¹, Amelia Szymanowska-Narloch², Rafał Dziadziuszko¹

¹Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland

²Department of Pneumology and Allergology, Medical University of Gdansk, Poland

Non-small cell lung cancer (NSCLC) driven by activating mutations in *epidermal growth factor receptor (EGFR)* constitutes up to 10% of NSCLC cases [1]. According to the NCCN guidelines, all patients (with the exception of smoking patients with squamous cell lung cancer) should be screened for the presence of activating *EGFR* mutations, i.e. deletion in exon 19 or point mutation L858R in exon 21, in order to select the group that benefits from EGFR tyrosine kinase inhibitors (EGFR TKIs) treatment. Among approved agents there are the 1st generation reversible EGFR TKIs, erlotinib and gefitinib, and the 2nd generation irreversible EGFR TKI, afatinib. The objective response rates to these drugs in randomised clinical trials were in the range of 56–74%, and the median time to progression 9–13 months [2–7]. These two classes of EGFR TKIs inhibit non-selectively both mutated and the wild type EGFR, which explains their main toxicities, i.e. trophic changes of the skin, nails, and the hair as well as gastro-intestinal symptoms, e.g. diarrhoea [8, 9].

The most common determinant of resistance to these drugs is the clonal expansion of cancer cells with T790M mutation (Thr790Met) in exon 20 of *EGFR* that is detected in 63–69% of the cases, irrespective of the class of EGFR TKIs used in the first line of treatment [10]. T790M variant decreases the affinity of the 1st and 2nd generation EGFR TKIs to EGFR ATP-binding pocket, which results in enhanced proliferation signalling and prompts disease progression. The efficacy of chemotherapy, e.g. platinum and pemetrexed doublet, after progression on EGFR TKIs is limited. The median progression-free survival in the AURA3 and IMPRESS prospective clinical trials was 4.4 and 5.4 months, respectively [11, 12]. Similarly, patients with EGFR activating mutations seem not to benefit from immune checkpoint inhibitors treatment [13].

Osimertinib (Tagrisso™), a 3rd generation, irreversible EGFR tyrosine kinase inhibitor, is selectively active against EGFR protein with activating mutations, including T790M resistance mutation to the 1st and 2nd generation EGFR TKIs. In the randomized phase III AURA3 trial, the median progression free survival, duration of response, and the rates of objective response were 10.1 months, 9.7 months and 71%, respectively [11, 14]. In comparison to chemotherapy osimertinib was more efficacious also in patients with central nervous system (CNS) involvement. In subgroup analysis, the benefit in patients with CNS metastases was similar to that seen in general population. Median progression free survival was 8.4 months, with the relative risk decrease of 68% (HR = 0.32) [11]. In experimental studies, osimertinib was shown to have a higher blood brain barrier penetrance in comparison to other EGFR TKIs (gefitinib, erlotinib, afatinib, rociletinib) [15].

Due to a strong affinity to the mutated EGFR protein osimertinib is very well tolerated. In AURA3 clinical trial treatment related adverse events in grade 3 or higher were noted in 23% patients treated with osimertinib

versus 47% in the group receiving cisplatin doublet [11]. Among the mild toxicities of osimertinib there were diarrhoea (41%; 1% grade ≥ 3), rash (34%; < 1% grade ≥ 3), dryness of skin (23%; 1% grade ≥ 3), and paronychia (22%). In the pooled analysis of the data from prospective trials, the frequency of interstitial lung disease (ILD) among the patients treated with osimertinib was 4% (grade 1, $n = 2$; grade 3, $n = 3$; and grade 5, $n = 3$) [16]. The incidence of this toxicity is similar as in the case of 1st and 2nd generation EGFR TKIs. Prolongation of QT was noted in 4% of patients receiving osimertinib, with only 1 case in grade 3 [11].

Although osimertinib is metabolised by CYP3A4, its inhibitors, e.g. itraconazole, do not significantly impact the drug's turnover [17]. On the other hand, strong inducers of CYP3A, e.g. rifampicin, carbamazepine or St. John's Wort, may cause significant reduction in osimertinib exposure and therefore their concomitant use should be avoided. Moderate inhibitors of CYP3A, e.g. bosentan, efavirenz, etravirine, modafinil may also increase osimertinib metabolism and should be therefore used with caution. In terms of interactions with commonly used drugs, Tagrisso can be safely combined with gastric acid reducing substances, e.g. omeprazole, as well as with simvastatin [18].

The presence of T790M mutation can be assessed in biopsied tumour tissue or in plasma through *liquid biopsy* that allows its detection in circulating cell free DNA (cfDNA). The latter method requires a standard collection of peripheral blood into an EDTA tube (purple or lavender cap tube, used for collecting blood for whole blood count analyses), and isolation of plasma through centrifugation within 3 hours. In Poland, T790M can be assessed in many academic centres and commercial laboratories. The companion diagnostic tests for osimertinib that were used in drug registration trials are Cobas EGFR Mutation Test and Cobas EGFR Mutation Test v2 for liquid biopsy. These real-time PCR based tests allow for detection of 42 mutations in *EGFR* exons 18, 19, 20 and 21, including T790M mutation. The sensitivity of T790M detection by liquid biopsy in reference to tissue biopsy is in the range of 61–70%, which implies that liquid biopsy negative result necessitates consideration for obtaining tumour tissue biopsy [19, 20]. For example, among 102 patients with the negative result of liquid biopsy, T790M was detected in tumour biopsy in 45 (44%) cases [20]. The median progression-free survival (PFS) in this group was 16.2 months, whereas in the group tested negative by both diagnostic modalities the median PFS was 2.8 months [20]. On the other hand, in phase 1/2 trial there were 21% of objective responses in patients in whom tissue biopsy tested negative for T790M mutation [14]. Most likely, at least in part of this group it would have been possible to detect mutation through liquid biopsy. In order to qualify a patient to osimertinib therapy it is sufficient to detect T790M mutation with one of these methods. Objective response rates to osimertinib of 64% were seen in prospective trials both in tissue and liquid biopsy groups [11, 19]. In cases when both tests have been performed, but only one yielding a positive result, treatment with osimertinib is justified.

There are other molecular methods for detection of T790M mutation, e.g. Sanger sequencing, next generation

sequencing and digital droplet PCR, the latter being the most sensitive. Some of these methods require a threshold value, above which the result is interpreted as “positive”. According to local expertise, these methods may also be used for evaluation of molecular resistance mechanisms in NSCLC patients after progression on 1st line EGFR TKIs.

In the following section, we present three cases that were successfully treated with osimertinib after progression on 1st and 2nd generation EGFR TKIs.

Case 1

A 63-year-old male (an ex-smoker that quit 20 years ago, with smoking history of 15 pack-years) was referred to our outpatient clinic with NSCLC diagnosis to assess treatment options. The tumour was located in the right lung and spread to the mediastinal and supraclavicular lymph nodes. The lesion was detected in the chest CT (April, 2015) performed due to recurring mild exertional dyspnoea, decrease in exercise tolerance and dry paroxysmal cough. On histopathological examination of mediastinal lymph nodes biopsy obtained at mediastinoscopy and the right supraclavicular lymph nodes from fine-needle biopsy metastatic lung adenocarcinoma (TTF1+, Napsin A+) was diagnosed (June, 2015). The patient denied any weight loss. His medical history included mild prostatic hyperplasia, past lithotripsy due to urolithiasis, and in his youth hepatitis A. He is a farm worker.

The results of laboratory testing were within normal limits. The chest CT revealed suspicious additional changes in the lung parenchyma as well as bone lesions suggestive of metastases. In PET scan distant metastases were ruled out, however, due to significant regional spread of tumour (stage IIIB) the patient was not eligible for radical radiotherapy. In parallel to the staging procedures, the status of EGFR activating mutations was assessed and the exon 19 deletion was detected. The patient was therefore started on afatinib 40 mg QD.

After 4 weeks of treatment the patient presented with a facial rash (grade 1). After 12 weeks of treatment diarrhoea ensued, however, the patient remained professionally active. Diet modification and loperamide as needed were advised. In the chest CT performed after 12 weeks of treatment there was a partial tumour response. With no laboratory abnormalities, the patient continued therapy for 12 months. The rash with no need of treatment persisted.

In August 2016 the patient experienced a pathological vertebral fracture with no evidence of lung cancer progression on chest imaging and no evidence of disease progression in the brain MRI. However, a few days later there appeared progressive paraparesis. The spine MRI revealed metastases in vertebral bodies of Th1, Th7 and Th8 with protrusion into the epidural space and spinal cord compression. The patient underwent neurosurgery (posterior decompression and C4-Th11 stabilisation), rehabilitation (physiotherapy and kinesiotherapy) and palliative radiotherapy (30 Gy in 10 fractions) for affected area. The treatment with afatinib was continued.

In December 2016 (15th month of afatinib treatment) the chest CT revealed progression of the disease in the lungs. Genetic examination of circulating free DNA (cfDNA) was performed and *EGFR* T790M mutation was found. In December 2016 the treatment with osimertinib 80 mg QD was initiated. The severity of the neurological deficits was slowly improving and the patient recovered the ability to move his legs. Follow-up chest CT, performed after 2 months of treatment, revealed partial regression. In the following examination further regression was observed, with the sum of measurable dimensions of the lesions reduced in size by 38%. Currently, the patient is still experiencing a clinical benefit after 8 months of osimertinib treatment.

Case 2

A 68-year-old never-smoking female was referred to our outpatient clinic due to the stage IV lung adenocarcinoma, with involvement of the right supraclavicular lymph nodes and pelvic bones. Microscopic diagnosis was obtained via bronchoscopic biopsy and further confirmed by histologic examination of the tissue material from core needle biopsy of the supraclavicular node. The medical history included hypertension, ventricular extrasystoles, secondary hypothyroidism (after partial thyroidectomy due to thyroid adenoma), degenerative spine disease and hypercholesterolemia. Cisplatin and pemetrexed were used as the 1st line treatment (from December 2010 to March 2011). Due to progression of the lesion in the right lung, the patient received four cycles of docetaxel (from July 2012 to September 2012) and, subsequently, the palliative radiation to the chest in February 2013.

In July 2013, the patient was diagnosed with liver metastases. The liver lesion biopsy revealed activating *EGFR* mutation (exon 19 deletion), and the patient was enrolled in the clinical trial OAM4971G, comparing combination of erlotinib and onartuzumab (monoclonal antibody blocking MET protein signalling) with erlotinib treatment only. During the study the patient developed facial rash (grade 1), recognized as associated with erlotinib treatment. In the chest and abdomen CT (September 2013 and November 2013) tumour partial regression was reported. There were no clinically significant abnormalities in laboratory testing.

In March 2014 the patient was informed about negative outcome of the clinical trial. Unblinding revealed that the patient was treated in placebo/erlotinib arm, and, therefore continuation of erlotinib 150 mg QD was offered. The patient did not report any further toxicity until April 2015, when G2 paronychia appeared. The skin changes were located around nail folds, mostly of left hand fingers, and required the use of amoxicillin with clavulanic acid.

In July 2015, after 24 months of erlotinib treatment, the progression of liver metastases was diagnosed. The patient was proposed 3rd line chemotherapy, i.e. paclitaxel 80 mg/m² weekly over 3 week-period and 1 week-break thereafter. The treatment resulted in partial response that was maintained until April 2016. Because of availability of osimertinib within extended access programme, liver me-

tastasis biopsy was performed, resulting in confirmation of T790M resistance mutation by Cobas test. In the abdomen CT (December 2016), further progression of liver metastatic lesions was confirmed, with lesions' dimensions of 60 x 67 mm and 24 x 36 mm, respectively.

In December 2016 the patient began treatment with osimertinib 80 mg QD. In the first follow-up abdomen CT after 8 weeks significant regression of liver metastasis was seen, with reduction of the sum of lesion dimensions by 48%. Currently, after 8 months of treatment the patient is not reporting any side effects. On the last imaging (July 2017) almost complete remission of the liver lesions and full control of the other foci was confirmed, after more than 6 years from the initial diagnosis of the metastatic lung cancer.

Case 3

In a never-smoking 52-year-old female, the lung cancer was detected during the diagnostic work-up for exertional dyspnea. In chest CT (April 2014) a tumour in the lower left lobe with accompanying left-sided hydrothorax were reported. Lung adenocarcinoma was diagnosed on histological examination of sections obtained through core needle biopsy, and *EGFR* activating mutation (deletion in exon 19) was confirmed. In May 2014 gefitinib 250mg QD was initiated, which led to the partial disease response. In June 2015, after around 13 months of treatment, progression in the left lung ensued. In subsequent video-thoracoscopy the metastatic nodules in parietal pleura were biopsied and T790M resistance mutation was confirmed.

In July 2015 the patient was enrolled into an expansion cohort of phase I trial assessing the clinical activity of rociletinib, a 3rd generation *EGFR* inhibitor. After 6 months of treatment, the patient reported conjunctivitis, prolongation of QTc in ECG (QTcB up to 482 ms) and hyperglycaemia, deemed as related to rociletinib. After 12 months of treatment in July 2016 multiple brain metastases were diagnosed. The experimental therapy was continued as the patient was benefiting from disease control in the lungs. In September 2016 the vision impairment ensued that required ophtalmological consultation. The surgical treatment was recommended because of the predicted high dynamics of this type of cataract. Due to increasing toxicity of rociletinib and central nervous system progression the patient was ultimately taken off the trial.

In view of osimertinib availability in extended access program, blood sample was taken to determine the resistance mutation to 1st and 2nd generation TKIs. In examination of plasma cell-free DNA T790M mutation was detected. In September 2016 the treatment with osimertinib 80 mg QD was started.

Since December 2016 the patient was receiving low molecular weight heparin in therapeutic doses, i.e. Clexane 100mg QD, because of the deep vein thrombosis recurrence requiring hospitalization. In the head and chest CT, performed 10 weeks after osimertinib initiation, almost complete remission of CNS metastases and further control of chest lesions were reported. The patient has completed

8 months treatment now and is not reporting any treatment related side effects.

Given the high clinical efficacy and beneficial toxicity profile of osimertinib, this drug is currently being investigated in the first line of treatment of advanced NSCLC with activating *EGFR* mutations. The available clinical data suggests high effectiveness of the agent in this setting. Median progression free survival and objective response rates in previously untreated NSCLC patients with activating *EGFR* mutations in expanded cohort from phase I trial AURA were 19.3 months and 77%, respectively [21]. During American Society of Clinical Oncology Annual Meeting 2017 (ASCO 2017) reports on mechanisms of resistance to osimertinib were presented. Among the most common molecular changes after progression on osimertinib (also detectable in liquid biopsy) was *MET* amplification, present in 30% of the cases [22]. In three of these patients partial response was attained after administration of *MET* inhibitor in conjunction with EGFR TKI, which suggests new treatment option for patients with *MET* amplification as a resistance mechanism. Another group of molecular determinants of resistance to osimertinib includes mutations within *EGFR*, e.g. C797S, and, in other genes, e.g. *PIK3CA* E545K, *BRAF* V600E, or *KRAS* G12S as well as amplification of *HER2* and *FGFR1* [23]. In patients with *HER2* amplification as a resistance mechanism to *EGFR* TKIs, the combination of trastuzumab and paclitaxel resulted in partial responses in 41% of the patients [24]. Moreover, in patients with oligo-progression on osimertinib, ablative therapy of up to five metastatic lesions (surgery or stereotactic radiotherapy) was safe and allowed for continuation of TKI treatment [25]. The results of the phase III FLAURA trial, assessing efficacy of osimertinib in comparison to 1st generation EGFR TKIs (gefitinib or erlotinib) in first line of treatment of NSCLC patients with activating *EGFR* mutations, are soon to be announced.

In summary, osimertinib provides a novel, highly efficacious treatment for NSCLC patients progressing on EGFR TKIs with T790M mutation confirmed as the resistance mechanism. The drug is also effective in patients with brain metastasis who exhausted possibilities of local ablative therapies. The presence of T790M can be determined in tissue or liquid biopsy obtained after progression on EGFR TKIs. Osimertinib has a favourable toxicity profile, with mild rash and diarrhoea being the most common.

The authors declare no conflict of interest.

References

- Pardinas JR, Xiao L, Zhang J, Li K. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005; 97: 339-46.
- Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJ-TOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11: 121-8.
- Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; 12: 735-42.
- Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EU-RTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13: 239-46.
- Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; 31: 3327-34.
- Wu YL, Zhou C, Liang CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol* 2015; 26: 1883-9.
- Kowalski DM, Krzakowski M, Ramlau R, Jaskiewicz P, Janowicz-Żebrowska A. Erlotinib in salvage treatment of patients with advanced non-small cell lung cancer: results of an expanded access programme in Poland. *Contemp Oncol (Pozn)* 2012; 16: 170-5.
- Jänne PA, Boss DS, Camidge DR, et al. Phase I dose-escalation study of the pan-HER inhibitor, PF299804, in patients with advanced malignant solid tumors. *Clin Cancer Res* 2011; 17: 1131-9.
- Yap TA, Vidal L, Adam J, et al. Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors. *J Clin Oncol* 2010; 28: 3965-72.
- Jenkins S, Chih-Hsin Yang J, Jänne PA, et al. EGFR mutation analysis for prospective patient selection in two Phase II registration studies of osimertinib. *J Thorac Oncol* 2017; 12: 1247-56.
- Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med* 2017; 376: 629-40.
- Soria JC, Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. *Lancet Oncol* 2015; 16: 990-8.
- Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early stage lung cancer evolution. *Nature* 2017; 545: 446-451.
- Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015; 372: 1689-99.
- Ballard P, Yates JW, Yang Z, et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. *Clin Cancer Res* 2016; 22: 5130-40.
- Yang JC, Ahn MJ, Kim DW, et al. Osimertinib in Pretreated T790M-Positive Advanced Non-Small-Cell Lung Cancer: AURA Study Phase II Extension Component. *J Clin Oncol* 2017; 35: 1288-96.
- Dickinson PA, Cantarini MV, Collier J, Frewer P, Martin S, Pickup K, Ballard P. Metabolic Disposition of Osimertinib in Rats, Dogs, and Humans: Insights into a Drug Designed to Bind Covalently to a Cysteine Residue of Epidermal Growth Factor Receptor. *Drug Metab Dispos* 2016; 44: 1201-12.
- Vishwanathan K, et al. Effect of food and gastric pH modifiers on the pharmacokinetics of AZD9291. *Mol Cancer Ther* 2015; Abstract: B153.
- Jenkins S, Yang JC, Ramalingam SS, et al. Plasma ctDNA Analysis for Detection of the EGFR T790M Mutation in Patients with Advanced non-small Cell Lung Cancer. *J Thorac Oncol* 2017; 12: 1061-70.
- Oxnard GR, Thress KS, Alden RS, et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2016; 34: 3375-82.
- Ramalingam S, Yang JC, Lee CK, et al. LBA1_PR: Osimertinib as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts. *J Thorac Oncol* 2016; 11 (4 Suppl): S152.
- Piotrowska Z, et al. MET amplification (amp) as a resistance mechanism to osimertinib. *J Clin Oncol* 2017; 35 (suppl): abstr. 9020.

23. Guibert NM, et al. Early detection of competing resistance mutations using plasma next-generation sequencing (NGS) in patients (pts) with EGFR-mutant NSCLC treated with osimertinib. *J Clin Oncol* 2017; 35 (suppl): abstr. 11529.
24. De Langen J, et al. Trastuzumab and paclitaxel in patients (pts) with EGFR mutated non-small-cell lung cancer (NSCLC) that express HER2 after progression on EGFR TKI treatment. *J Clin Oncol* 2017; 35 (suppl): abstr. 9042.
25. Kim C, Azuma K, Sakai K, et al. Local ablative therapy (LAT) for oligoprogressive, EGFR-mutant, non-small cell lung cancer (NSCLC) after treatment with osimertinib. *J Clin Oncol* 2017; 35 (suppl): abstr. e20545.

Address for correspondence**Rafał Dziaduszek**

Department of Oncology and Radiotherapy
Medical University of Gdansk
Skłodowskiej-Curie 3 A
80-210 Gdansk, Poland
e-mail: rafald@gumed.edu.pl

Submitted: 31.07.2017

Accepted: 10.09.2017