**Pharmacophore**

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

# EXCEPTIONALLY LONG SURVIVAL WITH LORLATINIB IN A PATIENT WITH ALK-REARRANGED LUNG CANCER

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**ARTICLE INFO**

**Received:**
27 Apr 2023
**Received** in revised form:
17 Jul 2023
**Accepted:**
19 Jul 2023
**Available online:**
28 Aug 2023

***Keywords:*** ALK, NSCLC, Lorlatinib, Case report, Cancer

**ABSTRACT**

Genetic abnormalities in the anaplastic lymphoma (ALK) kinase gene are present in 3-5% of Non-squamous Cell Lung Cancer (NSCLC) cases. ALK gene rearrangement plays a crucial role in determining the sensitivity of neoplastic cells to small molecule ALK tyrosine kinase inhibitors. However, some patients may develop resistance to ALK inhibitors over time, leading to disease progression. In such cases, it is important to perform genetic testing to identify any emerging mutations that may be responsible for resistance and to select the appropriate subsequent treatment. We provide a case of a 56-year-old patient with advanced NSCLC. The patient achieved an overall progression-free survival of 71 months, which highlights the potential benefits of using a sequence of ALK inhibitors in treating advanced ALK-rearranged lung adenocarcinoma. Overall, this case study highlights the importance of genetic profiling and personalized treatment in managing advanced NSCLC, and it offers hope for improved outcomes in patients with ALK-rearranged lung adenocarcinoma.



**To Cite This Article:** Szklener K, Nieoczym K, Niedziela K, Światłowski L, Mańdziuk S. Exceptionally Long Survival with Lorlatinib in a Patient with Alk-Rearranged Lung Cancer. Pharmacophore. 2023;14(4):1-5. https://doi.org/10.51847/n1YjZeJNBd

## Introduction

Genetic abnormalities in the anaplastic lymphoma (ALK) kinase gene are present in 3-5% of Non-squamous Cell Lung Cancer (NSCLC) cases [1-3]. Patients with the presence of ALK gene rearrangement are usually women or people in the younger age group, who never smoked [3, 4]. ALK gene rearrangement determines the sensitivity of neoplastic cells to small molecule ALK tyrosine kinase inhibitors (TKI-ALK) [2, 3]. TKI-ALK currently covers 3 generations of drugs, the use of which in the appropriate sequence seems to have an impact on the survival time of patients with primary disseminated NSCLC [3, 5, 6]. Despite many studies showing the sensitivity of cancer to the given inhibitors, most patients relapse [3, 5]. For this reason, it is often helpful to submit the biopsy material from the metastatic site for genetic testing [5, 7]. Emerging new treatment-resistant mutations have been observed, therefore the knowledge gained through genetic profiling may help select the appropriate treatment for patients who have progressed [3, 5, 6]. We present a case study in a patient with advanced ALK-rearranged lung adenocarcinoma treated with three generations of ALK inhibitors: crizotinib, alectinib, and lorlatinib with an overall progression-free survival (PFS) of 71 months [8, 9].

*Case Study*

In February 2017, a 56-year-old woman with no history of smoking was hospitalized with a diagnosis of adenocarcinoma of the right lung. The complaints of the patient included a chronic cough lasting for about 2 months. The imaging tests showed

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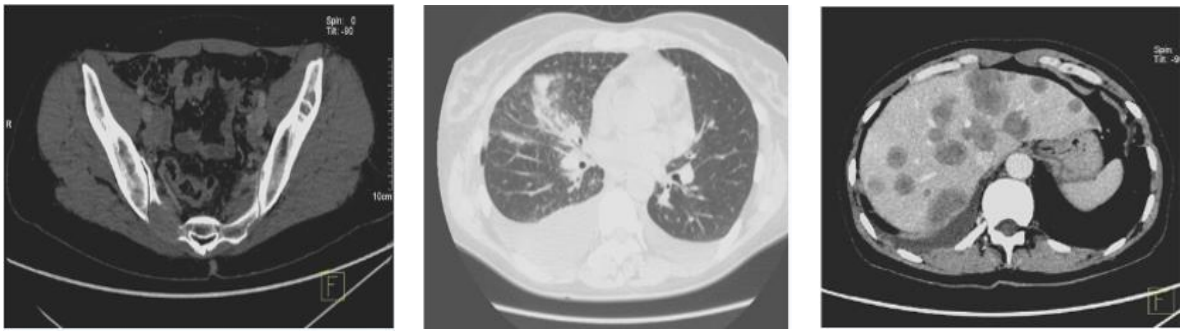
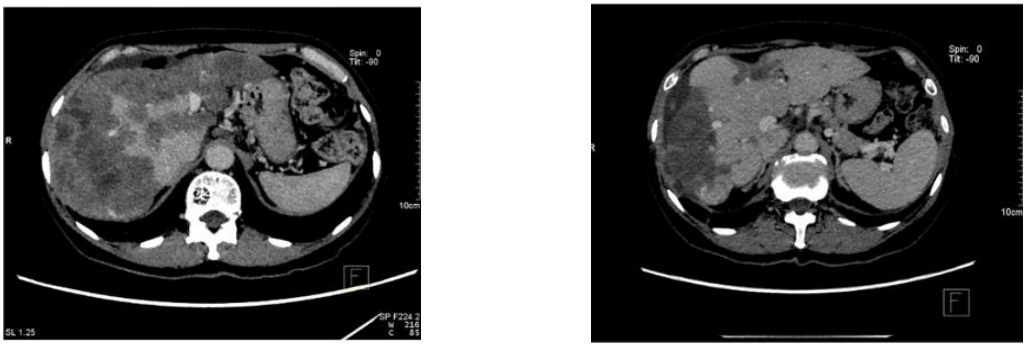
numerous metastatic lesions in the skeletal system and in the liver, which indicated the fourth stage of cancer advancement. The first head imaging examination revealed no Central Nervous System (CNS) metastasis **(Figure 1)**.



a) b) c)

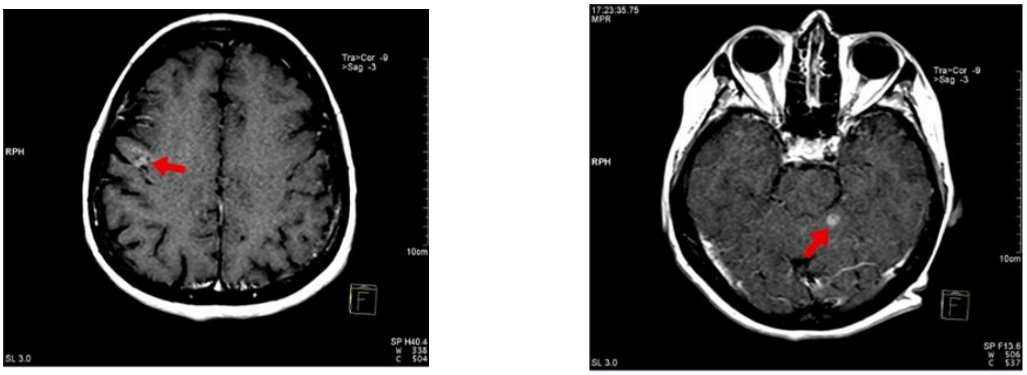
**Figure 1.** Presentation of the disease process before treatment. Metastatic lesions; a) the sacrum; b) the right lung; c) the liver.

Initially, chemotherapy was administrated, with Paclitaxel and Cisplatin in 3 cycles and additionally 1 pericardial cycle of Cisplatin. The information about the positive rearrangement status of the ALK gene in 76% of cell nuclei was obtained from the report of the genetic laboratory. Therefore, in April 2017, the patient qualified for targeted therapy with the 1st generation ALK inhibitor (Crizotinib, 200mg twice a day) and intravenous bisphosphonates. The patient continued the above-mentioned therapy until March 2020; when, after 36 months of treatment, control imaging studies described the progression of metastatic lesions in the liver, and physical examination showed ptosis, gait, and balance disturbances **(Figure 2)**. This suggested CNS involvement. In March 2020 four metastatic CNS lesions were confirmed by neuroimaging **(Figure 3)**. Then, the patient qualified for stereotaxic radiotherapy of the CNS lesions and the second-line treatment with the second-generation ALK inhibitor (Alectinib, 600mg twice a day). This led to obtaining a relatively long PFS (Progression Free Survival) of 6 months. In May 2020 stereotaxic irradiation of the metastatic lesion in the right frontoparietal area was performed, and a dose of 24 Gy was administered once using the VMAT technique.



a) b)

**Figure 2.** Metastatic lesions in the liver: a) February 2020; b) May 2020.

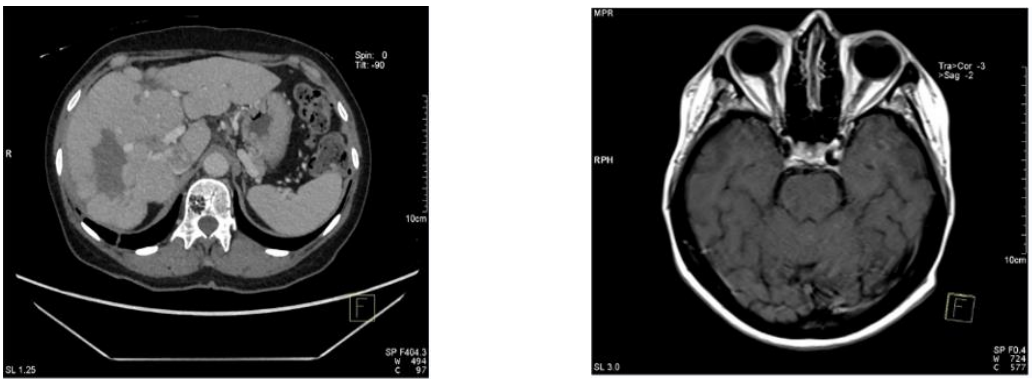


a) b)

**Figure 3.** Central Nervous System Metastases (CNS); March 2020.

In response to the subsequent progression of metastatic changes in the liver, the patient was qualified for treatment with a third-line, third-generation ALK inhibitor (Lorlatinib, 100mg daily) since October 2020. The primary tumor decreased in size

with Lorlatinib treatment, while the clinical symptoms improved and the disease was evaluated to be stable. Additionally, the brain lesions were still detectable but showed no growth **(Figure 4)**. During the treatment with Lorlatinib, there was an elevated level of lipaze in stage 3 after C8 of Lorlatinib. Over the course of treatment with ALK inhibitors, no side effects above Ist. toxicity according to CTCAE was observed. However, the patient was diagnosed with osteonecrosis of the jaw, in November 2021.



a) b)

**Figure 4.** Metastatic lesions during treatment with lorlatinib: a) the liver; b) the CNS

Neuroimaging was conducted in August 2022, and lesions in the liver were detected, which raised suspicion of metastatic changes. Therefore, a second liver biopsy was performed which confirmed the progression. Genetic examination, based on materials obtained from metastatic lesions, revealed the KLC-ALK gene fusion. Treatment with bevacizumab and lorlatinib was initiated leading to the stabilization of progressive changes. At the time of publication of the work, the PFS is at 71 months **(Figure 5)**.

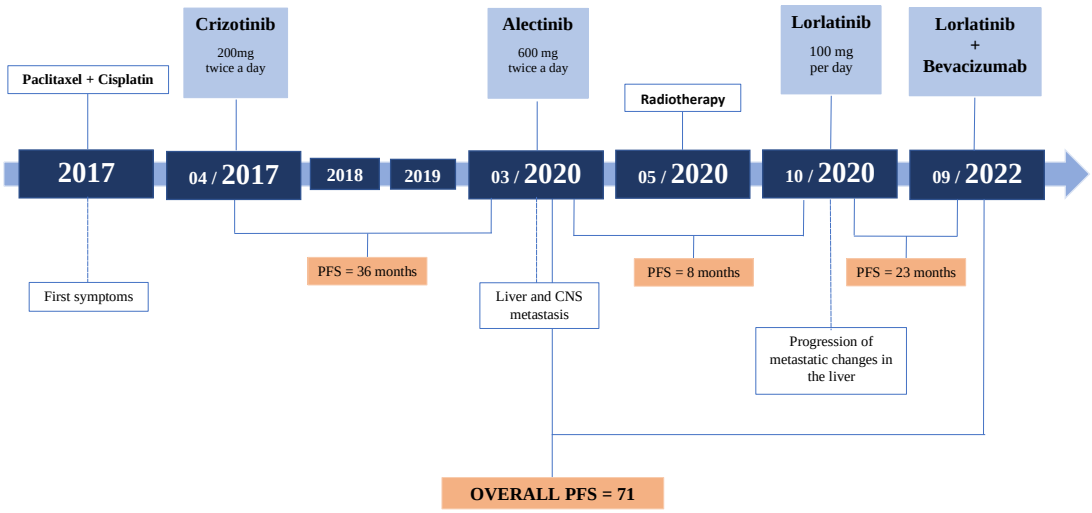



**Figure 5.** Timeline of events for a case study.

**Results and Discussion**

In our paper, we report spectacular treatment with lorlatinib with an overall PFS of 71 months (with the longest continuous PFS of 36 months), obtained due to the treatment with 3 sequentially following ALK inhibitors: crizotinib, alectinib, and lorlatinib. Lorlatinib is a drug recommended in patients who have progressed treatment with 1st and 2nd-generation inhibitors; additionally, it is more effective in the treatment of metastases in the central nervous system compared to other inhibitors [10-12]. In the case of our patient, due to progression during the use of lorlatinib, a repeated biopsy of liver lesions was performed and gene sequencing was performed using FoundationOne®CDx which is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes [13, 14]. Based on it, mutations in the KLC1-ALK fusion, ALK-SCAMP5 non-canonical fusion, and MDM2 amplification genes were revealed. The described mutations allow lorlatinib to be reused together with bevacizumab, to which cancer will be sensitive.

Bevacizumab is a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF) [15]. This drug crosses the blood-brain barrier. Studies have shown that when combined with targeted therapy or chemotherapy, it is effective in the treatment of brain metastases in the course of NSCLC [16].

Using the information collected so far and studies on the re-use of lorlatinib in patients who progressed after the initial treatment with lorlatinib [17], it was decided to start treatment with this third-generation inhibitor. Due to the rapid progress in NSCLC treatment, more and more patients can benefit from targeted therapies focused on specific types of mutations [3, 5]. Repeated biopsies allow for the detection of mutations, gene fusions, and molecular profiling of acquired resistance in patients who have been treated for NSCLC, making it possible to match the drugs better in case of progression [3, 5].

**Conclusion**

Based on the collected information, it can be concluded that currently, the most difficult challenge is the treatment of NSCLC with ALK gene rearrangement after treatment with lorlatinib, during which progressive lesions occurred.
In addition, the need to repeat biopsies in patients treated with targeted therapy is worth further discussion to control the emergence of new, treatment-resistant mutations and, on this basis, appoint other drugs sensitive to a given mutation or sensitization to a previously used drug.
Furthermore, these studies may indicate the benefit of using a higher-generation drug without prior use of a lower-generation drug or reusing a previously used drug.

**Acknowledgments:** We hereby express our deepest gratitude towards the Chair of Clinical Oncology and Chemotherapy and Department of Radiology, Medical University of Lublin Poland for the provision of workspaces and academic support.

**Conflict of interest:** None

**Financial support:** None

**Ethics statement:** None

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