



# UNIVERSITÀ DI PARMA

## ARCHIVIO DELLA RICERCA

University of Parma Research Repository

COVID-19 in lung cancer patients receiving ALK/ROS1 inhibitors

This is the peer reviewed version of the following article:

*Original*

COVID-19 in lung cancer patients receiving ALK/ROS1 inhibitors / Leonetti, A.; Facchinetti, F.; Zielli, T.; Brianti, E.; Tiseo, M.. - In: EUROPEAN JOURNAL OF CANCER. - ISSN 0959-8049. - 132:(2020), pp. 122-124. [10.1016/j.ejca.2020.04.004]

*Availability:*

This version is available at: 11381/2881518 since: 2022-01-09T21:28:38Z

*Publisher:*

Elsevier Ltd

*Published*

DOI:10.1016/j.ejca.2020.04.004

*Terms of use:*

openAccess

Anyone can freely access the full text of works made available as "Open Access". Works made available

*Publisher copyright*

(Article begins on next page)

## **COVID-19 in NSCLC patients receiving ALK/ROS1 inhibitors: Report of two cases**

Alessandro Leonetti,<sup>1,2</sup> Francesco Facchinetti,<sup>3</sup> Teresa Zielli,<sup>1</sup> Elena Brianti,<sup>4</sup> Marcello Tiseo<sup>1,2\*</sup>

<sup>1</sup> Medical Oncology Unit, University Hospital of Parma, Parma, Italy.

<sup>2</sup> Department of Medicine and Surgery, University of Parma, Parma, Italy.

<sup>3</sup> INSERM U981, Gustave Roussy Cancer Campus, Université Paris Saclay, Villejuif, France

\* Correspondance to:

Francesco Facchinetti, MD MSc.

Université Paris-Saclay, Institut Gustave Roussy, Inserm.

Biomarqueurs prédictifs et nouvelles stratégies thérapeutiques en oncologie.

114 Rue Edouard Vaillant, 94800 Villejuif, France.

Francesco.Facchinetti@gustaveroussy.fr

## **Introduction**

Since December 2019, an increasing number of coronavirus disease-19 (COVID-19) cases have been reported all around the globe following the outbreak of the pandemic acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.<sup>1</sup> To date, COVID-19 lacks a specific treatment to counteract the onset of SARS and subsequent multiorgan failure, whose evolution is usually rapid and severe. Liang and collaborators recently described an increased risk of COVID-19 among patients with cancer, which is also associated with a poorer COVID-19 prognosis.<sup>2</sup> Thus, international panels have recommended to delay or suspend anticancer treatments, when feasible, raising the issue of potential cancer progressions.<sup>3</sup> Concerning oncogene-addicted non-small cell lung cancer (NSCLC) patients, outcomes are strongly influenced by the continuous administration of targeted tyrosine-kinase inhibitors (TKIs). Thus, the withdrawal of TKI might be detrimental in this subgroup of patients. This becomes even more relevant when a pulmonary infection by SARS-CoV-2 is diagnosed accidentally in asymptomatic patients. Herein, we present two cases of oncogene-driven NSCLC patients suspected infected by SARS-CoV-2 who maintained targeted therapy with ALK/ROS1 TKIs in the presence of SARS-CoV-2 interstitial pneumonia and recovered from infection without specific antiviral treatments.

## **Case 1**

A former smoker 62-years old man was diagnosed with *ALK*-rearranged NSCLC in January 2020. A computed tomography (CT) scan performed in late December 2019 documented a tumor lesion in the right hilum and right lower paratracheal lymphadenopathy, associated with bilateral lung metastases. On January 31<sup>st</sup>, the patient started targeted therapy with alectinib for advanced disease. On March 16<sup>th</sup> the patient reported asthenia and dry cough, in absence of fever, which was treated with beclometasone/formoterol inhalations twice daily. Six days later (March 22<sup>nd</sup>), the patient developed ageusia, anosmia and night sweats, with concomitant resolution of cough. All the symptoms resolved on March 29<sup>th</sup> and did not require further medications. CT scan performed on March 30<sup>th</sup>, after two

cycles of alectinib, showed partial response of disease and, collaterally, the onset of slight bilateral subpleuric ground-glass opacities (Figure 1). Due to the lack of symptoms the patient was discharged without any specific medication and alectinib was continued. The test for SARS-CoV-2 was performed on RT-PCR on April 4<sup>th</sup>, and the result was negative. At the time of writing the manuscript, the patient was completely asymptomatic and was continuing targeted therapy.

## **Case 2**

A never smoker 52 years-old man was diagnosed with advanced ROS1-positive NSCLC in September 2015. The patient was currently undergoing lorlatinib from November 2019, following brain progression of disease after failure of previous crizotinib. Since the beginning, the treatment was well tolerated and the patient achieved metabolic complete response of thoracic disease with decrease of brain lesions in January 2019, which was still documented at the last radiological assessment performed in February 2020. On the 9<sup>th</sup> of March 2020, the patient reported fever (until 39° C) and dry cough, which worsened in the subsequent three days. After the admission to Emergency Service, a High-Resolution CT (HRCT) scan of the thorax (March 12<sup>th</sup>) showed the onset of multiple bilateral ground glass opacities, with a crazy paving pattern (Figure 2). RT-PCR performed on March 13<sup>th</sup> was negative for SARS-CoV-2. The patient was treated with antibiotic treatment with azithromycin and ceftriaxone for 10 days since March 12<sup>th</sup>, and lorlatinib treatment was not discontinued. Six days after the beginning of antibiotic therapy, the symptoms were improved and the patient was weaned completely off oxygen supply. C-reactive protein values, which were high at the time of admission to the hospital (49 mg/L), were normalized on March 20<sup>th</sup> (3 mg/L). Due to remission of symptoms, the patient was discharged on March 23<sup>rd</sup>.

## **Discussion**

To our knowledge, this is the first report of advanced NSCLC patients who carried on targeted therapy with ALK/ROS1 TKIs during SARS-CoV-2 pneumonia. In both our cases, the young age and overall

good performance status were two important factors which influenced the decision of continuing the therapy. However, we should note that the severity of COVID-19 in our reports was mild, and both patients did not require antivirals or (hydroxy)chloroquine.

Both of our cases were negative for SARS-CoV-2 tested on nasopharyngeal swab. In both cases nevertheless, symptoms, HRCT and laboratory findings were highly evocative for SARS-CoV-2 infection. While in Case 1 the SARS-CoV-2 test was performed once the infection was in remission, hence the negative result, we speculate that the SARS-CoV-2 test of the Case 2 was a false negative. Indeed, a not negligible rate of false negative results has been documented when assessing by RT-PCR, considering that this method heavily rely on the presence of viral genome at the site of sample collection and is operator-dependent.<sup>4</sup>

In a recent paper, Zhang and collaborators described a case of *EGFR*-mutated NSCLC patient who continued osimertinib during COVID-19. Similarly at our cases, the patient had a slight discomfort during the infection which not required intensive care, and he recovered from pneumonia following antiviral treatment with lopinavir/ritonavir.<sup>5</sup>

Considering that interstitial pneumonia is a rare albeit potentially severe adverse events in patients receiving ALK-TKIs, a differential diagnosis between SARS-CoV-2 manifestation and a TKI-induced side effect must be taken into account.<sup>6</sup> Since the radiological patterns of COVID-19 are evocative but not always diriment, a multidisciplinary discussion with radiologists is advisable in this subgroup of patients, and CT scan findings must be necessarily correlated with clinical and laboratory features. Even though the COVID-19 outcome in our patients who continued TKIs was favorable, we could not draw definitive conclusions. Large scale studies are urgently needed to assess whether or not TKIs should be maintained during SARS-CoV-2 pneumonia, especially when not severe, in order to avoid potentially-dangerous withdrawal of effective anticancer drugs.

**Figure 1.** CT scan of Case 1 (alectinib for *ALK*-positive NSCLC) treatment showed the onset of multiple bilateral subpleuric ground glass opacities in upper and lower lobes, suspicious for SARS-CoV-2 pneumonia.

**Figure 2.** CT scan of Case 2 (lorlatinib for *ROS1*-positive NSCLC) documented multiple bilateral subpleuric ground-glass opacities in a crazy paving pattern, highly suggestive for SARS-CoV-2 pneumonia.

## References

1. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. doi:10.1056/NEJMoa2001316
2. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337. doi:10.1016/S1470-2045(20)30096-6
3. Q&A on COVID-19 | ESMO. <https://www.esmo.org/newsroom/covid-19-and-cancer/q-a-on-covid-19>. Accessed April 2, 2020.
4. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clin Infect Dis*. March 2020. doi:10.1093/cid/ciaa310
5. Zhang H, Huang Y, Xie C. The Treatment and Outcome of a Lung Cancer Patient Infected with SARS-CoV-2. *J Thorac Oncol*. 2020;0(0). doi:10.1016/j.jtho.2020.02.025
6. Pellegrino B, Facchinetti F, Bordi P, Silva M, Gnetti L, Tiseo M. Lung Toxicity in Non-Small-Cell Lung Cancer Patients Exposed to ALK Inhibitors: Report of a Peculiar Case and Systematic Review of the Literature. *Clin Lung Cancer*. 2018;19(2):e151-e161. doi:10.1016/j.clcc.2017.10.008