

Fernando Barata, Henrique Queiroga, Encarnação Teixeira, Teresa Almodovar, Marta Soares, Barbara Parente, Juan Carlos Mellidez, Paula Alves, Ana Antunes contributed to revising the article critically for important intellectual content.

All the authors contributed to the final approval of the version to be submitted.

Funding

This work was supported by Roche.

Conflict of interests

The authors, F. Barata, H. Queiroga, E. Teixeira, T. Almodovar, M. Soares, B. Parente, J.C. Mellidez, P. Alves, declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

A. Antunes declares herself to be employee of Roche Farmacêutica Química which can be perceived an competing interest.

Acknowledgments

Medical writing and editorial assistance were provided by Catarina Alves, Medical Writer at Eurotrials, Scientific Consultants (now part of CTI Clinical Trial & Consulting Services), funded by Roche. Statistical support was provided by Vera Vicente, Senior Statistician at Eurotrials, Scientific Consultants (now part of CTI Clinical Trial & Consulting Services) and funded by Roche.

References

1. D'Addario G, Felip E, Group EGW. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2008;19 Suppl 2, ii39–40.
2. Peng M, Weng YM, Liu HL, Yang GF, Yao Y, Han G, et al. Clinical characteristics and survival outcomes for non-small-cell lung cancer patients with epidermal growth factor receptor double mutations. *Biomed Res Int.* 2018;2018:7181368.
3. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicen S, Szczesna A, Juhász E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2010;11(6):521–9.

4. De Greve J, Van Meerbeeck J, Vansteenkiste JF, Decoster L, Meert AP, Vuylsteke P, et al. Prospective evaluation of first-line erlotinib in advanced non-small cell lung cancer (NSCLC) carrying an activating EGFR mutation: a multicenter academic phase II STUDY in Caucasian patients (FIET). *PLoS One.* 2016;11(3):e0147599.
5. Zhou C, Wu Y-L, Chen G, Feng J, Liu X-Q, Wang C, 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(8):735–42.
6. Rosell R, Dafni U, Felip E, Curioni-Fontecedro A, Gautschi O, Peters S, et al. Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. *Lancet Respir Med.* 2017;5(5):435–44.
7. Cicen S, Geater SL, Petrov P, Hotko Y, Hooper G, Xia F, et al. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (IUNO study). *Lung Cancer.* 2016;102:30–7.

F. Barata^a, H. Queiroga^b, E. Teixeira^c, T. Almodovar^d, M. Soares^e, B. Parente^f, J.C. Mellidez^g, P. Alves^c, A. Antunes^{h,*}

^a Centro Hospitalar e Universitário de Coimbra, Portugal

^b Centro Hospitalar São João, Porto, Portugal

^c Centro Hospitalar Lisboa Norte, Lisboa, Portugal

^d Instituto Português de Oncologia Francisco Gentil, Lisboa, Portugal

^e Instituto Português de Oncologia Francisco Gentil, Porto, Portugal

^f Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal

^g Centro Hospitalar Baixo Vouga, Aveiro, Portugal

^h Roche Farmacêutica Química, Portugal

* Corresponding author.

E-mail address: ana.antunes@roche.com (A. Antunes).

6 November 2019

<https://doi.org/10.1016/j.pulmoe.2020.08.007>

2531-0437/ © 2020 Sociedade Portuguesa de Pneumologia.

Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Value of rebiopsy in advanced Epidermal Growth Factor Receptor mutated Non-Small Cell Lung Cancer: Real-world data



Letter to the Editor

Acquisition of Epidermal Growth Factor Receptor (EGFR) mutation resistance (mainly T790M) to EGFR tyrosine kinase inhibitors (TKI) occurs in about half of Non-Small Cell Lung Cancer (NSCLC) patients treated with TKI.¹ Mutational status is important to guide therapy.^{2,3} Pirker stated that while

tissue biopsy is currently the main source for molecular analyses, liquid biopsies will gain importance for diagnosis and disease monitoring in the future.⁴ The aim of this study was to analyse the value of liquid and tissue rebiopsy for evaluation of EGFR mutational status in a real-world setting.^{5,6}

We carried out a retrospective identification of patients tested for EGFR mutation at a Portuguese cancer center between January 2015 and October 2019. We collected clinical data from patients with advanced EGFR mutation NSCLC. Descriptive statistic was used to analyse patients' characteristics.

Of the 824 patients that were evaluated for EGFR mutation, 160 (19%) had EGFR-mutant NSCLC.

Table 1 Rebiopsy sites and T90M detection success rate.

1st rebiopsy site	Number of biopsies	T790M +
Tissue biopsy/cytology	25	11 (44%)
Bronchial tissue	13	8 (62%)
Pleural fluid	8	3 (38%)
Cerebrospinal fluid	2	0
Bronchial secretions	1	0
Thoracic Lymph node	1	0
Liquid biopsy	25	6 (24%)
2nd/3rd rebiopsy site	Number of biopsies	T790M+
Tissue biopsy/cytology	9	1 (11%)
Bronchial tissue	4	0
Pleural fluid	3	0
Brain	1	1 (100%)
Bone	1	0
Liquid biopsy	25	4 (16%)

Eighty-five of 160 patients (53%) had advanced disease (11 patients with stage III, 65 patients with stage IV and 9 patients presented a relapsing NSCLC). All neoplasms were adenocarcinomas due to a selection bias of our institution (only adenocarcinomas are tested for EGFR mutation). The median age at diagnosis was 69 years old [range: 39–95] and 66% of patients were female. History of tobacco use was reported as 42%.

The most common EGFR mutation was exon 19 deletion (del19) (33 patients) followed by L858R point mutation on exon 21 (24 patients) and del19 plus de novo T790M mutation (7 patients). Other uncommon mutations identified were L858R plus T790M, G719X on exon 18, del19 plus insertion of 20 and S7681 on exon 20 plus L858R.

Sixty-nine of 85 patients (81%) received EGFR-TKI and 46 patients (67%) developed disease progression on TKI. All 46 patients were submitted to a first (1st) rebiopsy, corresponding to a total of 50 rebiopsies: 25 liquid biopsies and 25 tissue biopsies/cytologies (some patients had both). Eighteen patients underwent a second and third (2nd/3rd) rebiopsy, corresponding to a total of 34 rebiopsies: 25 liquid biopsies and 9 tissue biopsies/cytologies.

The most common sampling method was liquid biopsy both for 1st (50%) and 2nd/3rd rebiopsies (74%). Bronchial tissue was the most common site for tissue biopsy/cytology followed by pleural fluid both in 1st and 2nd/3rd rebiopsies. Less common sites were cerebrospinal fluid, thoracic lymph nodes and bronchial secretions for 1st rebiopsy and brain and bone for 2nd/3rd rebiopsies.

We analysed the proportion of T790M mutation identified for each rebiopsy site as shown in Table 1.

In 1st rebiopsy, bronchial tissue was the site where T790M mutation was most frequently identified (62%), followed by pleural fluid (38%) and liquid biopsies (24%). No T790M mutation was identified in other sites, corresponding to a T790M mutation detection rate of 44% for 1st tissue rebiopsy.

In 2nd/3rd rebiopsy, T790M mutation was identified in the only brain biopsy performed and in 16% of the liquid biopsies. No T790M mutation was identified in other sites, meaning the detection rate for T90M mutation 2nd/3rd tissue rebiopsies was only 11%.

As shown in Fig. 1, 16 of 46 patients (35%) undergoing a 1st rebiopsy harbored a T790M mutation. Among the 30 remaining patients, 12 did not repeat biopsy and 18 were submitted to a 2nd/3rd biopsy. Five of those 18 patients (28%) were submitted to 2nd/3rd biopsies harbored a T790M mutation.

Furthermore, 18 of 46 patients undergoing rebiopsy presented exclusive intrathoracic disease. In this setting, T790M mutation was detected in 5 of 40 all rebiopsies (13%).

In patients with exclusive intrathoracic disease, liquid biopsy failed to identify T790M mutation, regardless of the number of rebiopsies. However, out of those 20 negative liquid biopsies, one had a positive matched tissue biopsy/cytology. T790M mutation was identified in 5 of 20 tissue rebiopsies/cytologies performed (25%).

Among 28 patients with extrathoracic disease, T790M mutation was detected in 17 of 44 rebiopsies performed (39%). T790M mutation was found in 10 of 30 liquid biopsies (33%) and in 10 of 14 tissue biopsies/cytologies (50%).

The overall survival was higher among patients submitted to rebiopsy [28.9 months (95%CI 21.2–35.0)] than among those were not [18.6 months (95%CI 9.87–NR)]. Although the increase of 10 months in overall survival was not statistically significant ($p=0.3116$), this lack of significance might be related with the small number of our cohort. Additionally, we may consider that this tendency towards overall survival benefit could be related with a better performance status of the rebiopsied patients (fit to receive treatment). Also, we can hypothesize that rebiopsy might guide the physician to choose the best treatment, which would lead to a better overall survival.

Our results suggest that 2nd/3rd biopsies are worth performing, as the proportion of patients with mutation identified is still significant and have a clinical impact in therapeutic choices and prognosis.⁷

T790M mutation is less identified in patients with exclusive intrathoracic disease. Liquid biopsy might not add value in this setting but tissue biopsy/cytology must be considered.

In extrathoracic disease, a higher proportion of T90M mutation was identified both in tissue biopsy/cytology and liquid biopsy. Although tissue biopsy/cytology was better than liquid biopsy, it is more difficult to perform and more invasive.

Furthermore EGFR mutant patients undergoing rebiopsy can present different resistance mechanisms, which reflects intratumoral and intertumoral heterogeneity, as well as dynamic changes in the relative populations of resistant clones over time.⁸

Despite the retrospective single center nature and small sample of our study, it is the first to present rebiopsy data of EGFR mutated NSCLC patients in Portugal and it is in line with other similar studies.^{9,10} Eun Kyong Goag et al. also reported a sample with a similar prevalence of EGFR mutations, with 561% in exon 19 del 34,1% in L858R or L861Q (compared with 47,8% of del19 and 34,8% in L858R in our sample) and the T790M mutation was identified in 43.9% patients with exon 19 del as the most significant factor affecting T790M mutation development (hazard ratio: 6.875, $P=0.014$). Similarly, our detection rate of T790M was 44% after the first tissue rebiopsy and the T790M mutation was detected in 50% of patients with an initial del19 mutation

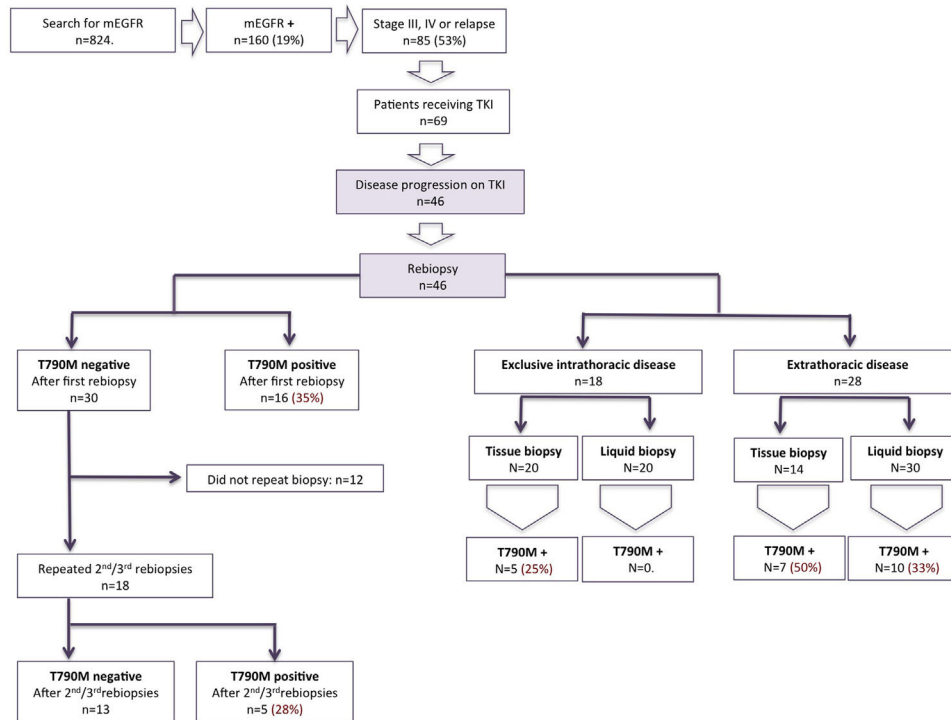


Fig. 1 Study flow chart.

Abbreviations: n: number of patients; N: number of biopsies.

(compared with 65% in Goag's study) and in 26% of patients with and an initial L858R mutation (vs. 21,5%).⁹ Similarly in another Japanese study, the T790M mutation was also more frequent with an exon 19 deletion mutation (63%) than in those with a L858R mutation (38%) ($p = 0.035$).¹⁰ Prospective, multicenter studies are needed to validate these findings.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

- Seto T, Nogami N, Yamamoto N. Real-World EGFR T790M testing in advanced non-small-cell lung cancer: a prospective observational study in Japan. *Oncol Ther* [Internet]. 2018;6(2):203–15, <http://dx.doi.org/10.1007/s40487-018-0064-8>.
- Cabanero M, Sangha R, Sheffield BS, Sukhai M, Pakkal M, Karsan A, et al. Management of EGFR-mutated non-small-cell lung cancer: practical implications from a clinical and pathology perspective. *Current Oncol*. 2017;24(2):111–9, <http://dx.doi.org/10.3747/co.24.3524>.
- Hong MH, Kim HR, Ahn B, Heo SJ, Kim JH, Cho BC. Real-world analysis of the efficacy of rebiopsy and EGFR mutation test of tissue and plasma samples in drug-resistant non-small cell lung cancer. *Yonsei Med J*. 2019;60(6):525–34, <http://dx.doi.org/10.3349/ymj.2019.60.6.525>.
- Pirker R. Conquering lung cancer: current status and prospects for the future. *Pulmonology*. 2020;26(5):283–90, <http://dx.doi.org/10.1016/j.pulmoe.2020.02.005>.
- Imakita T, Matsumoto H, Hirano K, Morisawa T, Sakurai A, Kataoka Y. Impact on prognosis of rebiopsy in advanced non-small cell lung cancer patients after epidermal growth factor receptor-tyrosine kinase inhibitor treatment: a systematic review. *BMC Cancer*. 2019;19(105):1–5, <http://dx.doi.org/10.1186/s12885-019-5309-x>.
- Saarenheimo J, Eigelienė N, Andersen H, Tirola M. The Value of Liquid Biopsies for Guiding Therapy Decisions in Non-small Cell Lung Cancer. *Front Oncol*. 2019;9(129):1–11, <http://dx.doi.org/10.3389/fonc.2019.00129>.
- Liu Y, Sun L, Xiong Z, Sun X, Zhang S, Ma J, Han C. Meta-analysis of the impact of de novo and acquired EGFR T790M mutations on the prognosis of patients with non-small cell lung cancer receiving. *Oncotargets Ther*. 2017;10:2267–79, <http://dx.doi.org/10.2147/OTT.S133082>.
- Piotrowska Z, Niederst M, Karlovich C, Wakelee H, Neal J, Mino-Kenudson M, Fulton L. Heterogeneity and coexistence of T790M and T790 wild-type resistant subclones drive mixed response to third-generation epidermal growth factor receptor inhibitors in lung cancer. *Cancer Discov*. 2015;5(7):713–22, <http://dx.doi.org/10.1158/2159-8290.CD-15-0399>.
- Goag E, Lee J, Chung K, Kim S, Leem A, Song H, et al. Usefulness of Bronchoscopic Rebiopsy of Non-Small Cell Lung Cancer with Acquired Resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor. *J Cancer*. 2018;9(6):1113–20, <http://dx.doi.org/10.7150/jca.21650>.
- Nosaki K, Satouchi M, Kurata T, Yoshida T, Okamoto I, Katakami N, et al. Re-biopsy status among non-small cell lung cancer patients in Japan: A retrospective study. *Lung cancer*. 2016;101:1–8.

R. Saúde-Conde^{a,*}, S. Cristóvão-Ferreira^a, E. Campoa^b,
M.T. Almodovar^c

^a *Medical Oncology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E., Lisbon, Portugal*

^b *Medical Oncology, Centro Hospitalar Universitário do Algarve, Faro, Portugal*

^c *Pulmonology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E., Lisbon, Portugal*

* Corresponding author.

E-mail address: rconde@ipolisboa.min-saude.pt (R. Saúde-Conde).

13 April 2020

<https://doi.org/10.1016/j.pulmoe.2020.11.004>

2531-0437/ © 2020 Sociedade Portuguesa de Pneumologia.

Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Secondary organizing pneumonia after Varicella-Zoster virus infection: a rare association



Dear Editor,

Organizing pneumonia (OP) is a histologic pattern of the lungs' response to a wide variety of insults, including infectious, non-infectious, or no apparent reason (cryptogenic).^{1,2} It is usually a great mimicker showing a wide variety of signs, symptoms, and high-resolution computed tomography (HRCT) findings, which makes it a frequent differential diagnosis. The usual distribution in the HRCT is patchy, peribronchiolar with the presence of numerous buds of granulation tissue within alveoli, often involving alveolar ducts and small airways; areas of consolidation are also the characteristics of organizing pneumonia.² Anatomopathological study is needed for final diagnosis.^{1,3,4} Although duration and initial symptoms depend on the underlying aetiology, OP usually presents with a several-month history of non-productive cough, low-grade fever, malaise, and shortness of breath. It is mostly seen in patients with pulmonary infection, drug reactions, transplantation, collagen vascular disease, granulomatosis with polyangiitis, after toxic-fume inhalation, e-cigarettes usage and, rarely, lung cancer of unknown primary site.^{1,5,6} When the underlying cause is not found, it is idiopathic and then called cryptogenic. Among the pulmonary infections, OP could be present after a bacterial, fungal, mycobacterial or even viral infection. Response to therapy is dependent on the treatment of the underlying cause but, usually, there is a good response to corticosteroid therapy with a good prognosis.^{3,4}

We report a case of a 35-year-old male, smoker of 15 packs per year, who went to the emergency department with pruriginous cutaneous eruption. Physical examination revealed vesicular cutaneous lesions, and on pulmonary auscultation a reduction of vesicular murmur and crepitations on the left hemithorax. Analysis identified respiratory failure, thrombocytopenia, hepatic dysfunction, and elevation of inflammatory parameters (C-Reactive Protein = 9.73 mg/dL (Normal < 0.5 mg/dL) with normal procalcitonin). The chest radiograph revealed bilateral opacities with air bronchogram (Fig. 1A). After the identification of epidemiological context for varicella-zoster infection (son with chickenpox), patient was admitted to hospital stay with the diagnosis of pneumonia due to

Varicella-Zoster virus and medicated with intravenous acyclovir and levofloxacin for 7 days. A good clinical, analytical, and imaging response was observed (Fig. 1B). During the hospitalization, a thoracic computed tomography (CT) scan was done, showing multiple small nodules scattered in the pulmonary parenchyma, some forming small conglomerates and surrounding ground glass. They presented bilateral distribution, but predominantly in the lower lobes. The largest conglomerate measured was 15 mm in diameter and was located in the lower-left lobe. (Fig. 1C). The patient was discharged asymptomatic.

After one year, the patient returned to the emergency department with fever, odynophagia, cough, and haemoptysis, showing no changes in physical examination or blood analysis. The following thoracic CT revealed a micronodular pattern with mostly calcified nodules. In the lower right lobe, a dense 19 mm nodule with ground-glass pattern and, juxtaposed to this, other calcified 19 mm and 5.8 mm nodules were found. There was a growth of the previously reported lesion in the lower-left lobe, which measured 21 mm. (Fig. 2A).

Blood and sputum culture were negative and bronchoalveolar lavage showed no changes. CT guided biopsy of the lower left lobe lesion was performed, with anatomopathological exam revealing focal lesions of organizing pneumonia with foamy macrophages in intralveolar localization (Fig. 2B). After the exclusion of other causes of organizing pneumonia and considering the previous diagnosis of varicella-zoster pneumonia, this cause was assumed. Corticosteroid therapy was started with an initial dose of oral prednisolone of 30 mg (0,5 mg/kg) daily for 6 months. Symptoms and imaging gradually improved and, after 1 year, clinical or imaging recurrence was not observed (Fig. 2C).

The present report describes a case of OP associated with varicella-zoster infection. Hypersensitivity pneumonitis (HP) could have a very similar clinical presentation such as fever, cough, and ground glass consolidations on CT and has a high incidence among Portuguese population in contact with birds, mould, cork or isocyanates.⁷ However, besides an identifiable exposure history, imaging changes are usually upper lobe predominant. Despite the usually good prognosis with response to antigen avoidance, some chronic forms, mainly fibrotic, could have the same prognosis as idiopathic pulmonary fibrosis.⁸ As previously stated, OP is an histological pattern associated with a variety of disorders,^{1,4} however, OP is rare after viral infections. There are a few cases reported of influenza