LETTER TO THE EDITOR

Inês Barreto*[1], Sara Figueiredo[2], Fernanda S. Tonin[3], Ana Sofia Variça[1], Direndra Hasmucrai[1], Paula Alves[1]

[1] Pulmonology Department, Centro Hospitalar Universitário Lisboa Norte
[2] Oncology-Medical Department, AstraZeneca Portugal
[3] Post-doctoral researcher, Health Technology Research Center, Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa

* **Corresponding author:** inesscbarreto@gmail.com

Keywords: *non-small-cell lung cancer; EGFR mutation; real-world data; tyrosine kinase inhibitors.*

Real-world challenges in first-line treatment of metastatic EGFR-mutated non-small cell lung cancer

Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), was recently introduced in several countries, including Portugal (reimbursement in 2021), as first-line treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating proto-oncogene epidermal growth factor receptor mutations (EGFRm)[1], after showing significant efficacy and safety when used in patients with EGFR-T790M resistance mutations[2,3]. However, despite advances in personalized target treatments in this field, challenges regarding patients' journey (e.g., therapy selection criteria, EGFR-TKI optimal sequencing, treatment beyond second-line) still exist[1].

Considering the scarcity of real-world evidence after the emergence of new EGFR-TKIs, we conducted a retrospective, single-center study (Lisbon-Portugal) to characterize a cohort of patients diagnosed between 01/2005-12/2021 and treated with first-line Osimertinib during the course of their disease (last follow-up: 06/2022). Disease and clinical outcome data were collected from medical/administrative records and summarized through descriptive statistics. Kaplan-Meier method was used to estimate progression-free (PFS) and overall survivals (OS). PFS was defined as the time between treatment initiation and the date of disease progression (evaluated every 12 weeks through computed tomography of thorax-abdomen-pelvis; brain metastases were assessed through brain CT scans and neurologic evaluation) or end of follow-up. OS was defined as the time between Osimertinib initiation and the date of death or end of follow-up, whichever occurred first. Patients who died before progression were censured. Results were reported as median and 95% confidence intervals; p-values below 5% were considered statistically significant (SPSS-Statistics-v.24.0).

Overall, 32 patients, mostly women (n=21, 65.6%), caucasian (n=30, 93.8%), non-smokers (n=22, 68.7%), with a median age of 70.0 (IQR 63.0-74.0; min-max: 45.0-97.0) were evaluated. Most patients presented an ECOG performance status of 0-1 (n=29, 90.6%). Simple mutations (n=26, 81.3%) were the most prevalent, particularly Exon 21-L858R and Exon 19-deletions (46.9% and 28.1%, respectively); around 85% of combined mutations also had Exon 21-L858R and Exon 19 deletions. Half the study population (50.0%) presented a PD-L1 TPS<1%. At diagnosis, all patients had adenocarcinoma, and most were classified with advanced

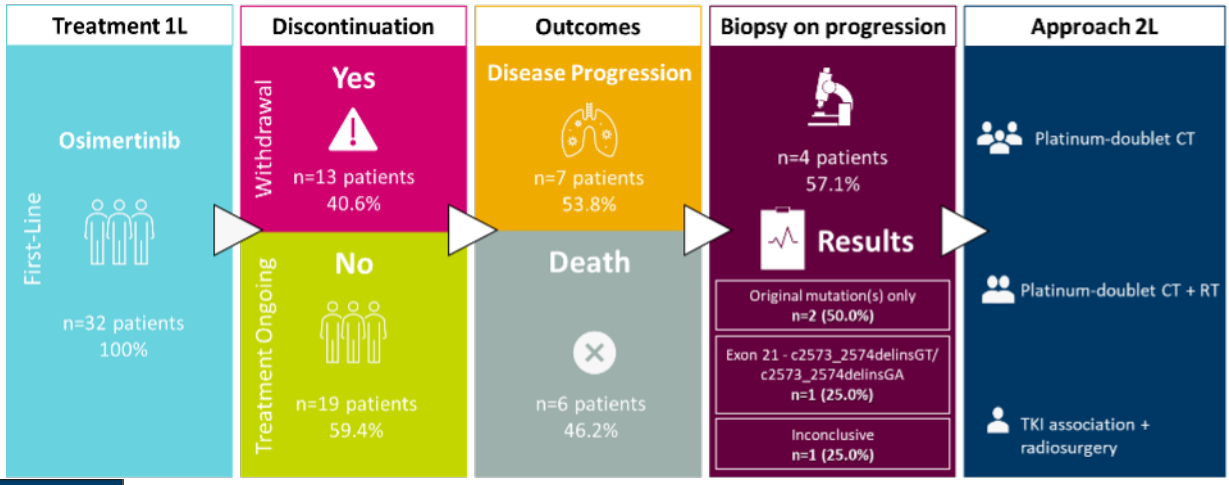


Figure 1 *Patients' journey.*

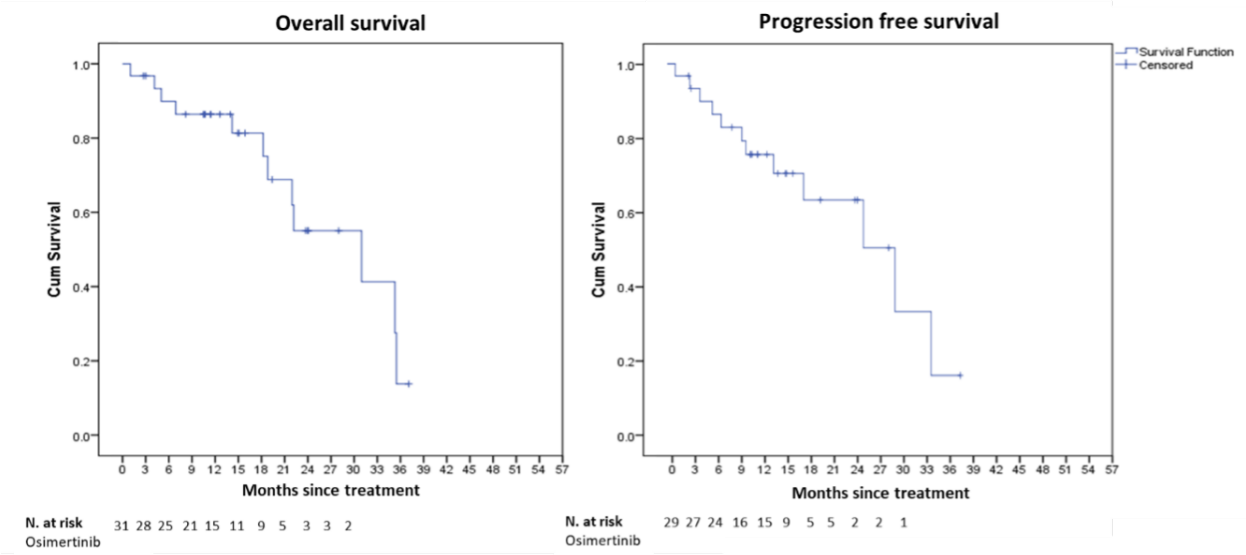
disease [stage IVA (n=8, 25.0%) or IVB (n=13, 40.6%)]. Among patients diagnosed with early stages (n=11, 34.4%), all were submitted to surgery (n=11, 100%). At the time of treatment initiation with Osimertinib, all patients presented at least one metastasis, mostly in bones (40.6%) and brain (31.3%). Although 14 patients (42.4%) were treatment naïve, the remaining had been submitted to previous treatments [surgery±adjuvant treatments (n=11), radiotherapy (n=4), radiotherapy+chemotherapy (n=2), and immunotherapy (n=1)]. Median follow-up since Osimertinib initiation was 15.0 months [IQR 10.5-22.5]; median treatment duration: 12.7 months [IQR 10.4-20.6].

Figures 1 and 2 summarize patients' journey and treatment outcomes, respectively. PFS and OS were not reached in our study due to the low number of events and sample size. Yet, findings are comparable to those from phase III FLAURA trial, which reassured the superiority and toxicity patterns of Osimertinib over first-generation EGFR-TKIs for EGFRm advanced NSCLC (PFS 18.9 vs. 10.2 months, respectively [HR 0.46; p<0.001]; OS 38.6 months vs. 31.8 months [HR 0.80; p=0.046])[4].

We also found that most patients (90.6%) presented controlled disease, either with partial response or stable disease (imaging data). Around 40% of the population discontinued treatment due to disease progression (n=7), disease-related death (n=5), or death due to toxicity [treatment-related pneumonitis] (n=1). Approximately 57% of patients that progressed (n=4/7) performed rebiopsy, with two of them (40.0%) presenting additional mutations (Figure 1). Patients who progressed were subsequently treated either with platinum-doublet chemotherapy (n=3), platinum-doublet chemotherapy+palliative radiotherapy (n=2), or TKI+radiosurgery (n=1). Although no significant differences between the overall population (n=32) and patients dying during the first six months of the study (n=8) were observed for most variables, there was a significantly higher number of stage IVA disease (p=0.043), and a tendency of worst performance status (ECOG 1-2) (p=0.064) among patients who died earlier (none of them was submitted to surgery; p=0.050).

We, thus, recommend further evaluations of the benefits of early treatment with EGFR-TKIs for patients with potentially worst prognosis (e.g., poorer performance status, stage IVA, unresectable disease). Grounded on the results from ADAURA trial, showing that Osimertinib significantly prolonged disease-free survival in stage IB-IIIA EGFRm NSCLC, this drug was recently approved in some countries as adjuvant therapy for this population (Ex19del or L858R) after complete tumor resection[5,6]. The meta-analysis from Li et al. 2022 (7 randomized trials; n=3,335) confirmed that Osimertinib tends to improve objective response and disease control rates (RR>1) as compared with other treatments and provides a significant protective factor for PFS and OS (HR <1; p<0.05), both when used as first, second, and third-lines/adjuvant therapy at different disease stages[3].

Nonetheless, ongoing concerns in this field refer to the increase of emerging acquired drug resistance mediated by loss of the EGFR-T790M mutation in patients using Osimertinib, including EGFR and non-EGFR-dependent mutations (e.g. ALK, BRAF, KRAS), MET amplification[7]. This highlights the role of mutational profiling/assessment before treatment selection and for patients with disease progression after first-line TKI. Moreover, tissue biopsies can provide complementary results for detecting mechanisms of resistance. Given the advantages of Osimertinib in NSCLC treatment, several ongoing trials (ELIOS-NCT03239340; ORCHARD-NCT03944772; SAFFRON-NCT05261399; SAVANNAH-NCT03778229) are assessing the feasibility of combining this therapy with other TKI, chemotherapies or signaling pathway inhibitors, especially after first-line progression. This could overcome multiple concomitant resistance mechanisms and guide treatment algorithms update. Further real-world analyses with longer



First-Line Treatment characterisation	Total n=32, n (%)
Response Evaluation	
DCR (Disease control rate)	29 (90.6%)
PR (partial response)	20 (62.5%)
SD (stable disease)	9 (28.1%)
PD (progressive disease)	3 (9.4%)
Treatment Discontinuation, n (%)	
Yes	13 (40.6%)
Death disease related	5 (38.5%)
Death due to toxicity	1 (7.7%)
Disease progression	7 (53.8%)
No	19 (59.4%)

Figure 2 *Outcomes associated with first-line treatment with Osimertinib.*

follow-up on Osimertinib use should be performed to strengthen this evidence.

Acknowledgments: The authors would like to acknowledge Dr. Fernanda Stumpf Tonin (FDR LDA company, Portugal) for medical writing support that was funded by AstraZeneca in accordance with Good Publications Practice (GPP3) guidelines.

1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (updated). European Society for Medical Oncology (ESMO) available at https://wwwesmoorg/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT-2020pdf 2020.
2. Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4(9):1046-61.
3. Li L, Huang Q, Sun J, Yan F, Wei W, Li Z, et al. Efficacy and safety of osimertinib for patients with EGFR-mutated NSCLC: a systematic review and meta-analysis of randomized controlled studies. Acta Oncol 2022;61(11):1347-53.
4. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378(2):113-25.
5. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383(18):1711-23.
6. Frampton JE. Osimertinib: A Review in Completely Resected, Early-Stage, EGFR Mutation-Positive NSCLC. Target Oncol 2022;17(3):369-76.
7. Mu Y, Hao X, Xing P, Hu X, Wang Y, Li T, et al. Acquired resistance to osimertinib in patients with non-small-cell lung cancer: mechanisms and clinical outcomes. J Cancer Res Clin Oncol 2020;146(9):2427-33.