A strategy to overcome *EGFR* p.T790M cis p.L792F induced resistance to osimertinib

Umberto Malapelle,[a]* *and Francesco Passiglia* [b]

[a]Department of Public Health, University of Naples Federico II, Naples, Italy
[b]Department of Oncology, University of Turin, San Luigi Hospital, Orbassano, Italy

eBioMedicine 2022;83: 104213
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.104213

Lung cancer is the leading cause of death for cancer worldwide.[1] From a histological point of view, non-small cell lung cancer (NSCLC) represents the vast majority (about 85%) of cases.[2] As a general rule, a high percentage of patients were diagnosed in advanced stages (IIIB/C-IV). In the past, for advanced stage NSCLC patients the only therapeutic choice was represented by chemotherapy. Currently, technological and therapeutic developments, with the introduction of tyrosine kinase inhibitors (TKIs) and immunotherapy, have led to a significant improvement in the survival outcomes of these patients.[3] The epidermal growth factor receptor (*EGFR*) gene mutations play a key role for the administration of EGFR-TKIs, and the advent of third-generation TKIs, such as osimertinib, define a new milestone in the upfront treatment of classical mutations subtypes (Exon 19 deletions and p.L858R) with a median patients' survival near to 40 months, as shown in the FLAURA clinical trial.[4]

However, the development of acquired resistances to upfront osimertinib represents a relevant clinical issue, and a deeper understanding of molecular alterations underlying resistance mechanisms is crucial to the development of biomarker-drive therapeutic strategies. Beyond the *EGFR* exon 20 p.C797S point mutations (Figure 1), a plethora of different alterations have been identified at the time of disease progression to osimertinib, leading to the investigation of novel drugs and combinations in the context of clinical trials.[5]

In this article of eBioMedicine, Sun and colleagues focused the attention on the role of acquired *EGFR* exon 20 p.L792F and the specific molecular mechanism by which this alteration induced resistance to osimertinib.[6] As a general rule, *EGFR* exon 20 p.L792F point mutation is generally found *in cis* with the *EGFR* exon 20 p.T790M, and according to the University of Texas MD Anderson Lung Cancer Moonshot GEMINI and Moffitt Cancer Center lung cancer databases, up to 26% of EGFR exon 20 p.L792X point mutations were discovered in *EGFR* exon 20 p.T790M positive patients treated with osimertinib.[7] Overall, *EGFR* exon 20 p.L792F point mutation inhibits the interaction between osimertinib and EGFR protein.[8] In their experience, the Authors showed that *EGFR* exon 20 p.L792F *in cis* with *EGFR* exon 20 p.T790M point mutation may represent an independent driver mutation. Based on the X-ray structure of osimertinib the Authors were able to predict that *EGFR* exon 20 p.L792F *in cis* with *EGFR* exon 20 p.T790M point mutation, is characterized in a blocker with a benzene or imidazole ring of hydrophobic side chain. In fact, the change of amminoacid in codon 792 strongly diminishes the affinity of osimertinib with the EGFR protein and is crucial to osimertinib resistance.[6] This mechanism seems to be related to the modification within tumor microenviroment (TME). The Authors showed that *EGFR* exon 20 p.L792F *in cis* with *EGFR* exon 20 p.T790M point mutation determines an upregulation of Jak and STAT3 phosphorylation and amplified IL-4 production. As a consequence, M2 macrophages polarization is promoted within TME,[9] resulting in osimertinib resistance.[6]

The identification of this mechanism may lead to the development of specific drugs useful in the treatment of advanced stage NSCLC patients who develop resistance after osimertinib administration. In particular, drugs able to target STAT3 with a subsequent inhibition of IL4 secretion and thus blocking M2 macrophages polarization may be adopted in this patient to overcome osimertinib resistance. Among these drugs, dupilumab seems to be promising in asthma and atopic dermatitis,[10] but a possible adoption in advanced stage NSCLC patients need to be confirmed by clinical trials.

The findings reported in this interesting paper add to our knowledge relevant data to better understand the relationship among *EGFR* exon 20 p.L792F *in cis* with *EGFR* exon 20 p.T790M point mutation, TME and osimertinib resistance mechanism. Prospective clinical trials evaluating STAT3 inhibitors with a subsequent inhibition of IL4 secretion and thus blocking M2 macrophages polarization are welcomed.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2022.104200

*Corresponding author at: Department of Public Health, University of Naples Federico II, Naples, Italy.
E-mail address: umberto.malapelle@unina.it (U. Malapelle).

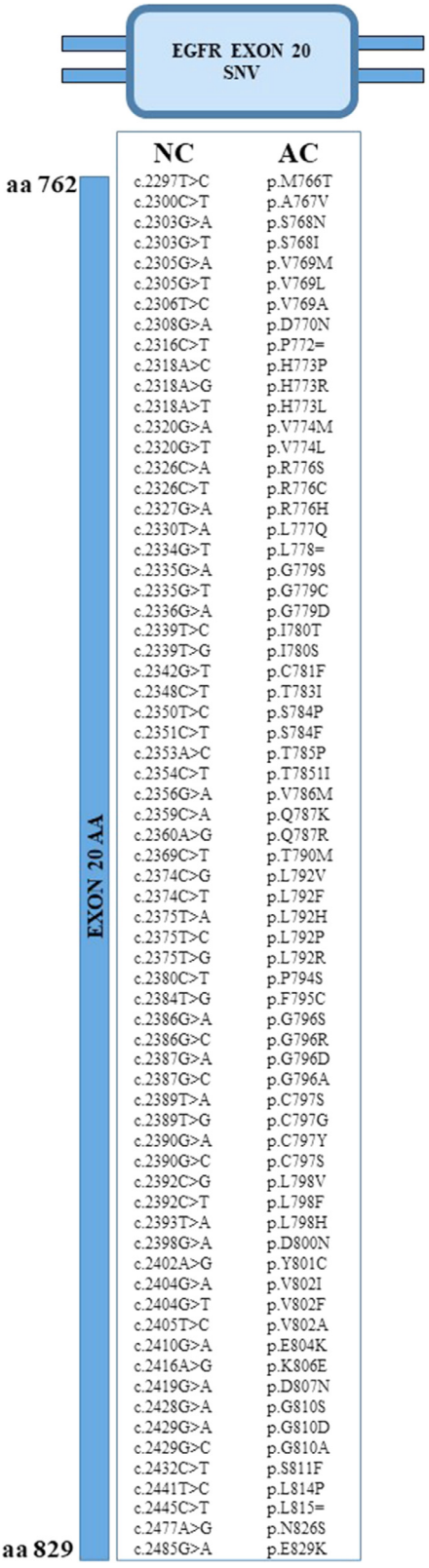

Figure 1. In the figure were reported the complete list of *EGFR* exon 20 point mutations (COSMIC, last access 07/26/2022).

Contributors

U.M. and F.P. Conceptualization, writing, editing and project administration.

Declaration of interests

Umberto Malapelle has received personal fees (as consultant and/or speaker bureau) from Boehringer Ingelheim, Roche, MSD, Amgen, Thermo Fisher Scientifics, Eli Lilly, Diaceutics, GSK, Merck and AstraZeneca, unrelated to the current work. Francesco Passiglia declared consultant's fee from: AstraZeneca, Amgen, Janssen.

References

1 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA*. 2022;72(1):7–33.
2 Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. *J Thorac Oncol*. 2022;17(3):362–387.
3 Kerr KM, Bibeau F, Thunnissen E, et al. The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. *Lung Cancer*. 2021;154:161–175.
4 Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *New Engl J Med*. 2018;378(2):113–125.
5 Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, & Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*, 2019;121(9):725–737.
6 Sun Y, Dong Y, Liu X, Zhang Y, Bai H, Duan J. Blockade of STAT3/IL-4 overcomes EGFR T790M-cis-L792F-induced resistance to osimertinib via suppressing M2 macrophages polarization. *eBioMedicine*. 2022. https://doi.org/10.1016/j.ebiom.2022.104200.
7 Le X, Puri S. Negrao MV, et al. Landscape of EGFR-dependent and -independent resistance mechanisms to osimertinib and continuation therapy beyond progression in EGFR-mutant NSCLC. *Clinic Cancer Res*. 2018;24(24):6195–6203.
8 Zhang Q, Zhang XC, Yang JJ, et al. EGFR L792H and G796R: two novel mutations mediating resistance to the third-generation EGFR tyrosine kinase inhibitor osimertinib. *J Thorac Oncol*. 2018;13(9):1415–1421.
9 Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clinic Investig*. 2012;122(3):787–795.
10 Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *New Engl J Med*. 2018;378(26):2486–2496.