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CORRESPONDENCE

Molecular predictors of *EGFR*-mutant NSCLC transformation into LCNEC after frontline osimertinib: digging under the surface

With the introduction of the third-generation tyrosine kinase inhibitor (TKI) osimertinib for the first-line treatment of epidermal growth factor receptor (*EGFR*)-mutant non-small-cell lung cancer (NSCLC), understanding underlying mechanisms of resistance becomes crucial in order to optimize treatment strategy. Histological transformation towards both small-cell lung cancer (SCLC) and squamous cell carcinoma have been described as resistance patterns featuring peculiar molecular landscapes, potentially detectable at diagnosis and becoming clinically evident after clonal selection and disease evolution.[1,2] To date, only anecdotal reports have described the histological transformation to large-cell neuroendocrine carcinoma (LCNEC) after EGFR TKIs, but no data on molecular profiling have been reported.

An 80-year-old Caucasian man, former light smoker, presented in January 2019 with persistent fever, despite antibiotic therapy. A total-body computed tomography (CT) scan and a fluorine-18 fluorodeoxyglucose positron emission tomography revealed a right upper lobe mass, with bilateral hilar and mediastinal lymph nodes, and a single bone lesion at the sternal body. In March 2019, biopsy of both the lung mass and the sternal lesion were diagnostic for lung adenocarcinoma (stage IVa; cT2aN3M1b), harboring an *EGFR* exon 19 deletion (*E746_A750del*). Next-generation sequencing (NGS) (FoundationOne CDx, Penzberg, Germany) confirmed the presence of an *EGFR* exon 19 deletion and revealed *TP53* (tumor protein p53), *RB1* (retinoblastoma), *PTEN* (phosphate and tensin homolog gene) and *CHEK2* (checkpoint kinase) mutations, as well as *NKX2-1* (NK2 homeobox 1 gene) and *TERC* (telomerase RNA component) amplification. From March 2019 to May 2020, he received first-line osimertinib 80 mg once daily, experiencing partial response (PR) as best response, with a progression-free survival of 15 months. In May 2020, the CT scan revealed bilateral enlargement of internal mammary lymph nodes; re-biopsy revealed metastasis of neuroendocrine carcinoma characterized by medium and large cells, supporting the diagnosis of LCNEC. NGS analysis of the new disease site showed the same genomic alterations detected at baseline, with the addition of *AKT* and *BCL2L2* (Bcl-2-like 2) amplification. Osimertinib was interrupted and the patient was treated with carboplatin-etoposide, experiencing PR after 3 months (Figure 1).

To the best of our knowledge, this is the first report of transformation into LCNEC after first-line osimertinib. Tissue-based molecular profiling performed at baseline and at disease progression suggests that LCNEC transformation might be triggered, and potentially predicted, by molecular mechanisms similar to those observed during SCLC evolution, i.e. *TP53* and *RB1* inactivation.[3] In addition, NGS analysis revealed the presence of molecular alterations frequently detected in LCNEC, such as *PTEN* mutation and *NKX2-1* amplification.[4]

Recent data indicate that intrinsic heterogeneity and pre-existent subclones might predict the main mechanism(s) leading to osimertinib resistance at later timepoint.[5] In this specific case, we might speculate that a subclonal cell population harboring molecular biomarkers of neuroendocrine differentiation present at the baseline and not detectable upon conventional histological examination, underwent progressive clonal evolution under the selective pressure of EGFR TKI treatment, finally leading to a pathological transition towards high-grade LCNEC. Baseline molecular heterogeneity, particularly the presence of molecular stigmata of potential transformation into high-grade neuroendocrine carcinoma (*TP53* and *RB1* alterations), might support the upfront application of broad, NGS-based, genomic profiling and would constitute a potential biological rationale for treatments combining chemotherapy and EGFR TKIs in such cases.[5]

L. Belluomini[1], A. Caliò[2], R. Giovannetti[3], M. Motton[4], R. Mazzarotto[5], C. Micheletto[6], M. V. Infante[3], A. Scarpa[2], M. Milella[1†]* & S. Pilotto[1†]

[1]*Section of Oncology, Department of Medicine, University of Verona School of Medicine and Verona University Hospital Trust, Verona;*
[2]*Section of Pathology, Department of Diagnostic and Public Health, University of Verona School of Medicine and Verona University Hospital Trust, Verona;*
[3]*Thoracic Surgery Department, University of Verona School of Medicine and Verona University Hospital Trust, Verona;*
[4]*Radiology Department, University of Verona School of Medicine and Verona University Hospital Trust, Verona;*
[5]*Section of Radiotherapy, Department of Surgery and Oncology, University of Verona School of Medicine and Verona University Hospital Trust, Verona;*
[6]*Pulmonary Unit, University of Verona School of Medicine and Verona University Hospital Trust, Verona, Italy*
(*E-mail: michele.milella@univr.it).

†Equal contribution (these authors share last co-authorship).

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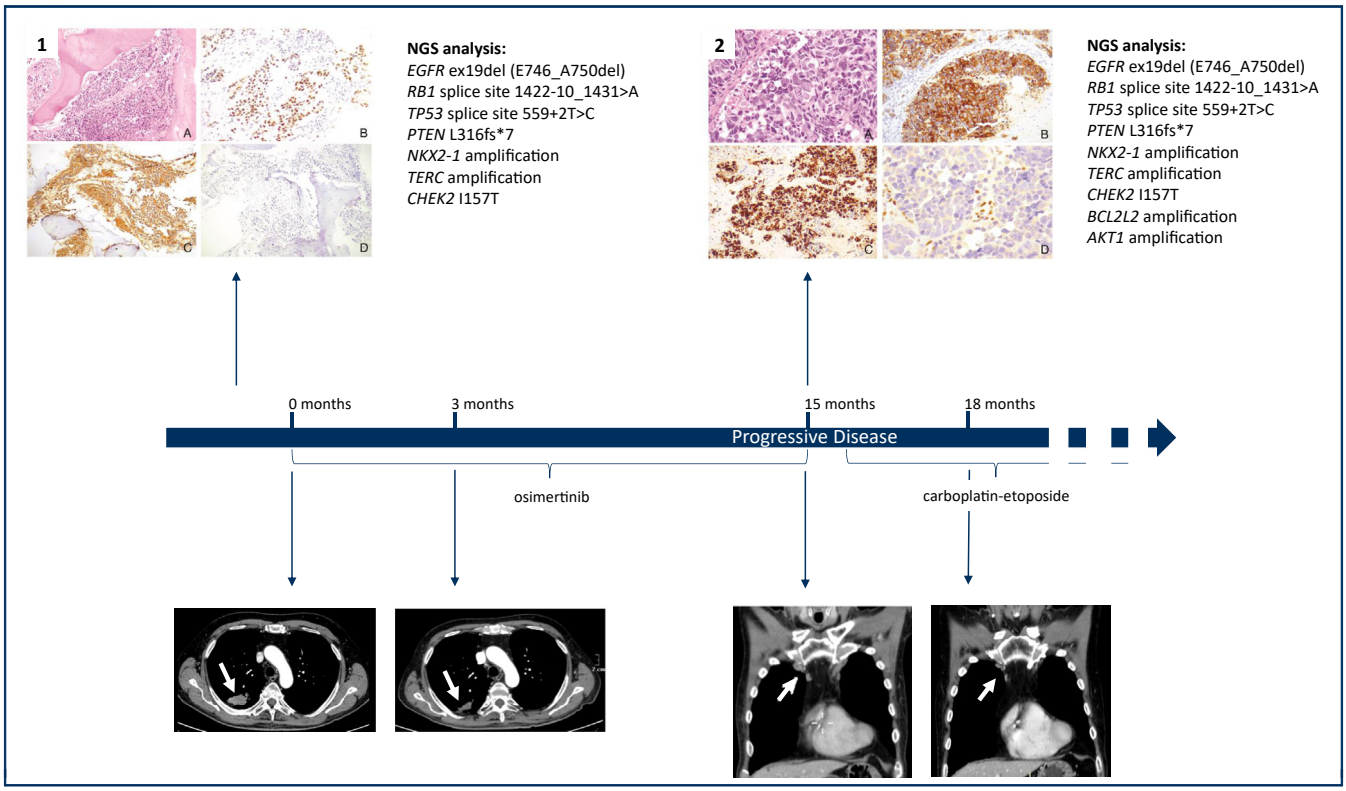

Figure 1. Disease evolution during treatment and clinical history.
Upper panel: morphological, immunohistochemical and NGS features of diagnostic biopsy (1) and of biopsy taken at progression (2). (1) Bone metastasis of lung adenocarcinoma on hematoxylin—eosin (A), with positive immunolabelling for TTF1 (B) and napsin (C), and negative for synaptophysin (D). NGS analysis was performed on the lung biopsy specimen. (2) Lymph node metastasis of large cell neuroendocrine carcinoma on hematoxylin—eosin (A); immunostaining for synaptophysin (B) and Ki67 (C); loss of staining for Rb in the neoplastic cells with internal positive control cells (D). Lower panel: on the left, CT scan images show primary right upper lobe mass before and after 3 months of osimertinib, with evidence of partial response. On the right, a new CT scan reveals disease progression at bilateral internal mammary lymph nodes; radiological evaluation demonstrates PR after 3months of carboplatin-etoposide. Arrows indicate target lesions.
BCL2L2, Bcl-2-like 2; *CHEK2*, checkpoint kinase; *EGFR*, epidermal growth factor receptor; *NGS*, next-generation sequencing; *NKX2-1*, NK2 homeobox 1 gene; *PTEN*, phosphate and tensin homolog gene; Rb, retinoblastoma protein; *RB1*, retinoblastoma gene; *TERC*, telomerase RNA component; *TP53*, tumor protein p53.

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