Editorial

Clinical outcomes provide new insights into transformation to small-cell lung cancer of pulmonary EGFR-mutant adenocarcinoma

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Despite very high response rate (RR) and significant clinical benefit of EGFR-tyrosine-kinase inhibitors (TKIs) in patients with advanced *EGFR*-mutated (*EGFR*M+) non-small cell lung cancer (NSCLC) of adenocarcinoma (LAC) type, virtually all cases become resistant to these drugs with a median progression-free survival (PFS) of 9–13 months. Thus, understanding the resistance mechanisms is crucial for identifying new treatments that can revert or delay this problem. A variety of mechanisms accounting for acquired resistance to the currently clinically used three generations of EGFR-TKIs have been uncovered (1-4). These include TKI-specific "on target" events, such as TKI-binding-impeding secondary or tertiary *EGFR*-mutations (e.g., T790M or C797S), *EGFR*-amplification (i.e., "too much target") or loss of target-mutation, and several EGFR-independent mechanisms affecting EGFR-TKIs of all three generations. The latter comprise the activation of alternative by-pass signaling pathways operating down-stream or in parallel with EGFR and phenotypic tumor changes, such as the transformation to small-cell lung cancer (SCLC), the epithelial-mesenchymal transition, or the trans-differentiation to squamous-cell carcinoma (1-4).

The transformation to SCLC is the most common of these histological changes and can occur in 3–10% of TKI-treated *EGFR*M+ LACs (1,2,5,6). Yet, rare cases of *de novo* *EGFR*M+ SCLC or mixed LAC-SCLC occurring in non-smokers independently of EGFR-TKI treatment and characterized by rapid progression have been described (5-7). Thus, it has been debated whether treatment-naïve disseminated *EGFR*M+ LACs may already contain TKI-resistant cells with a SCLC phenotype, which can be further selected and give rise to a genetically similar SCLC upon EGFR-TKI treatment, or alternatively, LAC cells are forced to change their phenotype by TKI-treatment as adaptive phenomenon (8). Although it can be difficult in routine clinical practice to determine whether the LAC-to-SCLC transformation is pre-existing or induced by the TKI-treatment (9), there is mounting evidence for a dynamic molecular and cellular plasticity between LAC and SCLC, including the notion of a common origin from pluripotent alveolar cells (5,6). Several aspects concerning the biology behind the SCLC-transformation of *EGFR*M+ LAC have been unraveled, but less is known regarding the clinical course and outcome of TKI-treated NSCLCs undergoing this transformation, as clinical data derive from case reports or small case series.

However, Marcoux *et al.* (10) recently published the outcomes from a large retrospective cohort of 67 *EGFR*M+ advanced lung cancers that either had phenotypically transformed to or were initially diagnosed as SCLC or large-cell neuroendocrine carcinoma (LCNEC) and had been treated between 2006 and 2018 at eight North American cancer centers. Specifically, the cohort comprised 57 cases initially diagnosed with LAC and one with NSCLC not otherwise specified that after having received systemic therapy (range, 1–6 lines, median, 2 lines), including at least one line of EGFR-TKIs, had transformed to SCLC in 55 cases, to LCNEC in two cases,

and to mixed SCLC-LCNEC in one patient. The utilized EGFR-TKIs were either erlotinib, afatinib or osimertinib and more than one TKI was administered in 40% of cases. Additionally, nine patients who had not received EGFR-TKIs but were diagnosed with *de novo EGFR*M+ SCLC or mixed NSCLC-SCLC were included, by considering these tumors as bona fide transformed LACs within a common biologic continuum. Resembling the mutation distribution of *EGFR*M+ LACs in general, *EGFR* exon 19dels and L858R had been detected as founder mutation at baseline in 69% and 25% of all patients, respectively, while the remaining 6% harbored less common founder *EGFR*-mutations, such as S768I, G719X or L861Q. In two patients an additional *de novo* T790M mutation was identified. Also baseline demographics of the whole cohort resembled those of the general population of patients with *EGFR*M+ LAC, as it consisted of 38 women and 29 men presenting with a median age at diagnosis of 56 years, no smoking history in 73% of cases, and Asian or Caucasian ethnicity in 42% and 49% of cases, respectively. Conversely, one feature that appeared specific to the cohort was that mutations in *TP53* and *RB1* were identified in 100% (7/7) and 50% (2/4) of baseline tumor specimens analyzed by next-generation sequencing (NGS). Given the historical material, pathology reports describing transformed or *de novo* tumors by histological features and/or positive immunohistochemistry (IHC) for at least one of three conventional neuroendocrine markers were available for only 59 of the 67 reviewed patients, with supplementary Ki-67 proliferation index registered in 32 cases. Likewise, the cases had been genotyped by different methods, including allele-specific polymerase chain reaction (PCR) assays, NGS, and whole-genome sequencing (WGS). Nonetheless, for some of the older cases residual tissue specimens allowed more comprehensive genetic reassessment, so that eventually genotyping of variable extent performed on transformed or *de novo* SCLC specimens was available for 59 of the 67 cases.

The time from initial diagnosis of advanced lung cancer to the onset of SCLC phenotype was 17.8 months (range, 2–60 months) and of EGFR-TKI treatment before transformation was 15.8 months (range, 1.3–53.4 months). Platinum-etoposide was expectedly the most used post-transformation therapy and resulted in a notable RR of 54% and a median PFS of 3.4 months among 48 assessable patients, which confirms it as valid initial therapeutic choice after transformation. Similarly, the RR among 20 assessable patients receiving taxanes, mostly late in the course and as single-agent, was 50% and the median PFS 2.7 months, with objective responses in patients treated with paclitaxel or nab-paclitaxel but not docetaxel. However, these relatively few cases and archival tissue biopsies from mostly single sites could not clarify whether the significant RR of taxanes was due to residual responsive LAC clones in transformed tumors or to specific sensitivity of the SLC-transformed cells. After transformation, EGFR-TKIs were administered to 52% of the patients, mostly in combination with or after cytotoxic chemotherapy, and some clinical benefit was perceived in three of four cases, in which reappearance of LAC histology could be documented in progressing sites after SCLC development. This is consistent with previous cases and suggests the co-existence of different growing SCLC- and LAC-clones in same patients (9). In contrast, no clinical response was observed in the 17 patients, who received immune checkpoint inhibitors, which seems to mirror the lack of efficacy of immunotherapy in the general population of *EGFR*M+ LAC (11,12). The median overall survival (OS) since initial diagnosis of advanced lung cancer and after SCLC-transformation was 31.5 and 10.9 months, respectively, which together with the frequent but transient responses to platinum-etoposide and a common metastatic spread to CNS detected after transformation (69% of 59 assessed patients) resemble the clinical behavior of classic smoking-associated SCLC with wild-type (wt) *EGFR*. Aptly, a previous literature review of 39 TKI-treated SLC-transformed LACs (37 were *EGFR*M+, 2 *ALK*-positive) and a recently retrospectively collected European cohort of 48 SCLC-transformed *EGFR*M+ LACs have shown data comparable to those of Marcoux *et al.* in terms of time to transformation since initial LAC diagnosis or after TKI-start, RR to platinum-etoposide, and OS since LAC diagnosis or after transformation (13,14).

Notably, all transformed cases undergoing genotyping maintained their founder *EGFR*-mutation, which is consistent with previous reports of SCLC-transformation in TKI-treated LACs (5,6,9,13,14). Some reports also indicated that the transformed cases became insensitive to EGFR-TKIs at least in part by downregulating EGFR expression rather than by acquiring a secondary T790M mutation (5,6,9). Similarly, Marcoux *et al.* found that 15 of their 19 cases with previously detected T790 (two *de novo* and 17 acquired during TKI-treatment) had lost T790 after transformation, though EGFR expression was not assessed (10). Nonetheless, these and the previous data suggest that the T790M gatekeeper mutant may reside in a clone different from the SCLC-transformed clone and may become dispensable for TKI-resistance after the phenotypic

transition. The authors propose that this may reflect a clonal diversion of the SCLC clone and the T790M clone from a common founder LAC population (10), in keeping with the branching evolutionary history of *EGFR*M+ lung LAC described by Lee *et al.* (15).

In line with the baseline data, the genotyping also showed that transformed and *de novo* SCLC samples frequently harbored mutations in *TP53* (79% of all tested cases, 91% of those tested by NGS), *RB1* (58%), and *PIK3CA* (27%). This is consistent not only with these mutations typically occurring in classic smoking-related *EGFR*-wt SCLC (16), but also with previous detection of these mutations in cases of LAC undergoing SCLC-transformation following TKI-therapy (5,6). Recent WGS analysis depicting the clonal origin and branching evolution of *EGFR*M+ LAC transforming to SCLC corroborated that *TP53* and *RB1* inactivation may predispose to SCLC-transformation, as TKI-resistant SCLC clones were found to originate from the founder LAC clones earlier (even before TKI-treatment) and much more frequently in cases with completely inactivated *RB1* and *TP53* at baseline (15). In these cases, the risk of SCLC-transformation was increased >40 times compared to LACs with intact Rb1 and p53 function (15). Thus, evaluating the mutational status of *TP53* and *RB1* at baseline might aid in predicting which LACs are more susceptible of SCLC-transformation after receiving EGFR-TKIs. Yet, how the presence of *TP53*- and *RB1*-mutations in *EGFR*M+ LACs correlates with the time to transformation remains unclear, not least because in several cases this time is of many months, suggesting that additional genetic/epigenetic changes are needed for the transformation to occur (13,17). It is also noteworthy that 4 of Marcoux and coworkers' cases harbored *MYC*-amplification (10), which is another recurrent genomic event of conventional smoking-induced SCLC (16). Conversely, 5 of the transformed cases displayed *EGFR*-amplification more characteristic for LAC, in addition to the founder *EGFR*-mutation (10), suggesting that both EGFR-downregulation and -upregulation may represent events contributing to the unresponsiveness of transformed tumors to EGFR-TKIs. Presumably, the above-mentioned recurrent alterations of *TP53*, *RB1*, *PIK3CA* and *MYC* could also promote TKI-resistance in the transformed tumor, given that these genes regulate a plethora of mechanisms related to cell proliferation and survival operating down-stream EGFR. This issue needs to be addressed in further studies.

Although limited by its retrospective character, lack of standardized treatment and response evaluation, and lack of uniform pathological analysis and genotyping of samples, the cohort published by Marcoux *et al.* (10), because of its size, provides valuable conclusions on appropriate treatments and prognostic implications for *EGFR*M+ LACs transforming to SCLC. It also illustrates how these tumors present clinical and genetic features reminiscent of both *EGFR*M+ LAC and classic smoking-related SCLC and emphasizes the importance of tumor re-biopsies at progression for the histological identification of phenotypic changes that are not yet identifiable by less invasive liquid biopsies. Moreover, together with previous studies, it indicates that TKIs, despite not being essential for the phenotypic change of tumor cells, may act as factors promoting SCLC-transformation, especially in NSCLCs harboring *TP53* and *RB1* mutations. However, additional relevant clinical and genetic aspects need to be addressed in the future. As only one patient in Marcoux *et al.*'s cohort received osimertinib as first-line therapy (10), it remains to be investigated prospectively what is the impact of first-line osimertinib on the occurrence of SCLC-transformation. An unsolved issue is also the role in SCLC-transformation of *EGFR*-mutations, given that they are considered early clonal events involved in the initiation of EGFR-driven LAC, thus justifying the significant TKI-responses detectable across multiple cancer sites (18). Yet, SCLC-transformation has occasionally been reported in *EGFR*-wt LAC and in *ALK*-rearranged LACs (13,14), suggesting that *EGFR*-mutations may function more as a predisposing than inducing element of transformation. Accordingly, some data suggest that SCLC-transformation occurs more rapidly in *EGFR*M+ than *EGFR*-wt LAC, but after transformation response to platinum-etoposide and OS are similar in the two groups and mimic those in conventional SCLC (14). Whether responses to different regimens of SCLC-transformed *EGFR*M+ LACs are associated with specific founder *EGFR*-mutations is also unexplored. Finally, though available data validate platinum-etoposide as clinical choice, more effective and targeted treatments are desirable for these challenging tumors. In this respect, standardized multigene analyses should be performed at baseline to address whether specific genetic signatures of *EGFR*M+ LAC may predispose to SCLC-transformation and contain potential therapeutic targets.

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