How can better identification of T790M help to inform treatment sequencing decisions in *EGFR* mutation-positive non-small-cell lung cancer?

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“Optimizing the detection of T790M after progression on first-/second-generation TKIs should allow more patients to benefit from subsequent osimertinib treatment.”

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The availability of three generations of *EGFR* tyrosine kinase inhibitors (TKIs) with different clinical profiles has revolutionized the treatment of *EGFR* mutation-positive (*EGFR*m+) non-small-cell lung cancer (NSCLC). Compared with the first-generation *EGFR* TKIs, erlotinib and gefitinib, head-to-head trials have shown improved efficacy with the second-generation irreversible ErbB family blockers, afatinib and dacomitinib, and the third-generation irreversible *EGFR* wild-type sparing TKI, osimertinib [1–3]. Unfortunately, despite high initial response rates with *EGFR* TKIs, acquired resistance is inevitable regardless of the choice of first-line TKI. Although other mechanisms exist, the discovery that the predominant mechanism of resistance to first- and second-generation *EGFR* TKIs is the ‘gatekeeper’ T790M mutation (~50–70% of cases) [4,5] prompted the development of third-generation, T790M-directed *EGFR* TKIs. Osimertinib, which is active against both *EGFR*-sensitizing and T790M-resistance mutations, was initially approved in the second-line setting based on remarkable activity in patients with metastatic *EGFR*m+ NSCLC after failure of first-line TKIs [4,6].

Given that osimertinib use in second line requires the presence of T790M, it is imperative for tumors to be characterized for molecular aberrations at the first manifestation of progression, to inform decisions about appropriate subsequent therapy [7]. Optimizing the detection of T790M after progression on first-/second-generation TKIs should allow more patients to benefit from subsequent osimertinib treatment [8]. Liquid biopsies offer the potential for easier, noninvasive mutation testing compared with tissue biopsies, which can also be challenging in clinical practice due to patient ineligibility, tumor inaccessibility and insufficient tissue availability [8]. Additionally, liquid biopsy avoids challenges associated with tumor heterogeneity, which can mean that mutations are missed if tissue biopsy is taken from a single tumor region [9]. On the other hand, tissue biopsy offers histological analysis of the tumor, and is generally more sensitive than current liquid biopsy assays which can produce false-negative results. Consequently, current guidelines recommend that negative findings by liquid biopsy should be followed-up by confirmatory tissue rebiopsy [10]. Where possible, all possible detection methods should be employed, using the most sensitive technique(s) available. In this regard, methods such as droplet digital PCR (ddPCR) and next-generation sequencing offer greater sensitivity and specificity compared with liquid biopsy methods [8,11].

In a recent analysis using both liquid biopsy (ddPCR) and tissue rebiopsy, the T790M mutation was identified in 49/67 patients (73%) who progressed on afatinib, including 36/54 patients (67%) after first-line afatinib [8]. This is consistent with previous reports which estimated the prevalence of T790M to be approximately 50–70% following progression on first-generation *EGFR* TKIs or afatinib [4,5]. The ddPCR technique used in the recent study was highly sensitive, which is likely to explain the high rate of T790M detection [8]. Indeed, a separate analysis comparing ddPCR with the US FDA-approved, semiquantitative PCR-based Cobas[®] *EGFR* Mutation Test v2

found generally high concordance, but the T790M positivity rate in patients who progressed during EGFR TKI treatment was 66% by ddPCR compared with only 24% according to the Cobas test [12]. Ultimately, these findings support the hypothesis that most patients will develop T790M-acquired resistance following progression on afatinib and will be eligible for subsequent osimertinib treatment, providing the right test is used. Subsequent osimertinib treatment in patients with T790M-acquired resistance to first-/second-generation EGFR TKIs achieved response rates of >70%, independent of T790M copy number [7,8]. These are important findings as they suggest that second-line osimertinib may be effective even in patients with subclonal T790M-positive tumors [8].

Despite the lack of prospective data on sequential EGFR-TKI treatment, retrospective analyses of the LUX-Lung 3, 6 and 7 trials (afatinib), and from ARCHER 1050 (dacomitinib) also suggest that sequential treatment with second-generation TKIs followed by osimertinib may be feasible and effective. Among 37 patients who received osimertinib after afatinib in a pooled analysis of LUX-Lung 3, 6, and 7, the median time on osimertinib was 20.2 months and median overall survival (OS) was not reached after a median follow-up of >4 years; 3-year OS was >90% [13]. Likewise, in 22 patients who received a third-generation EGFR TKI following dacomitinib in ARCHER 1050, median OS was encouraging, at 36.7 months [3].

Real-world outcomes in 204 patients with T790M-positive NSCLC, who received sequential afatinib and osimertinib, were assessed in the recent retrospective, observational GioTag study [14]. Median time on treatment was 27.6 months overall, 30.3 months in patients with exon 19 deletion (Del19)-positive NSCLC, 36.4 months in patients with Del19-positive NSCLC with Eastern Cooperative Oncology Group (ECOG) performance status 0/1, and 46.7 months in Asian patients. The study enrolled a broad patient population, including patients with ECOG performance status ≥ 2 (median time on treatment: 22.2 months) and patients with stable brain metastases (median: 19.4 months). These findings suggest that sequential afatinib and osimertinib can enable prolonged chemotherapy-free treatment in patients with T790M-acquired resistance, with a wide range of baseline characteristics.

Numerous factors must be acknowledged when considering the choice of EGFR TKI in any line of treatment. Given the high rate of CNS progression in patients with *EGFR*^{wt} NSCLC, it is noteworthy that afatinib and osimertinib appear to penetrate the blood–brain barrier more effectively than first-generation TKIs (no data are available for dacomitinib). Indeed, both afatinib and osimertinib have shown activity against existing CNS lesions and in reducing the risk of CNS progression [5,15]. These data provide support for afatinib and osimertinib as first-line treatments of choice in patients with brain metastases, and suggest that sequential afatinib and osimertinib can be recommended for patients with and without CNS metastases [16].

Second-generation EGFR TKIs have a broader inhibitory profile than first-generation EGFR TKIs, which means that they are active against many uncommon and compound *EGFR* mutations, as well as common mutations (Del19/exon 21 substitution L858R) [9]. In addition to extending the range of patients for whom first-line afatinib is effective, its broader inhibitory profile may help to delay the expansion of heterogeneous resistant subclones during progression, resulting in more homogeneous T790M-positive clones compared with those that arise following resistance to first-generation EGFR TKIs. This is supported by preclinical observations [9] and could potentially contribute to prolonged responses to second-line osimertinib [17], as well as facilitating detection of the T790M mutation by tissue or liquid biopsy.

For patients with T790M-negative tumors, subsequent treatment options are more limited, although alternatives to standard platinum-based chemotherapy are now being identified. While immuno-oncology drugs have generally shown little benefit in patients with *EGFR*^{wt} NSCLC, exploratory analysis of the Phase III IMPower150 study showed the combination of atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP) to have robust clinical activity after progression on EGFR TKIs [18]. Among 124 patients with *EGFR* mutations, OS and progression-free survival (PFS) were improved versus BCP, particularly in 91 patients with sensitizing *EGFR* mutations (OS, hazard ratio [HR]: 0.31; 95% confidence interval [CI]: 0.11–0.83; PFS, HR: 0.41; 95% CI: 0.23–0.75). Specific data in patients with T790M-negative disease are needed to determine whether this treatment may be effective in this population. One regimen that has shown promise in patients with T790M-negative NSCLC is afatinib plus bevacizumab. In the Phase II ABC study in patients with *EGFR*^{wt} NSCLC with acquired resistance to EGFR TKIs, treatment with afatinib/bevacizumab resulted in response rates of 14.3 and 22.2% in patients with T790M-positive and T790M-negative tumors, respectively, with median PFS times of 6.3 and 7.1 months [19]. The afatinib/bevacizumab combination could, therefore, be a salvage option for patients with T790M-negative NSCLC.

Of course, osimertinib is now established both as a first-line and a second-line option for the treatment of T790M-positive tumors, having demonstrated an impressive PFS benefit versus first-generation TKIs in the Phase III FLAURA trial [2]. Nevertheless, it is important to consider that mechanisms of resistance to osimertinib are

more heterogeneous than for first- and second-generation *EGFR* TKIs. Next-generation sequencing analysis of FLAURA samples indicated that the most common mechanism of resistance to first-line osimertinib ($n = 91$) was *MET* amplification (15%), followed by C797S in 7%, but no putative resistance mechanism was identified in >60% of tumors [20]. Thus, currently, no standard targeted treatment is available following osimertinib failure, and most patients will proceed to chemotherapy. This has led physicians to question whether long-term benefit could be better achieved by reserving osimertinib for second-line use, to prolong the chemotherapy-free period. However, it must be acknowledged that not all patients will develop T790M-positive tumors, and a proportion (i.e., those with T790M-independent resistance mechanisms) would not be eligible to receive and benefit from osimertinib if it was not given up front [5]. Thus, there is a risk in retaining osimertinib for second-line use. If a sequencing approach is adopted, the patient must be monitored closely for disease progression, and all possible testing methods for T790M must be applied.

In summary, further research is needed to define the optimal treatment sequence to maximize long-term survival, while maintaining quality of life. This will be facilitated by further development of highly sensitive and specific, noninvasive diagnostic techniques to optimize *EGFR* mutation testing.

Author contributions

MJ Hochmair was responsible for the conception and design of the work, participated in drafting the work or revising it critically for important intellectual content, approved the submitted manuscript and agrees to be accountable for all aspects of the work.

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MJ Hochmair has received honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, and Roche, and has had consulting or advisory roles with Boehringer Ingelheim, Merck Sharp & Dohme, Novartis and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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