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letter to the editor

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Reply to the letter to the editor 'Prevalence of rare EGFR mutations in non-small cell lung cancer: a multicenter study on 3856 Polish Caucasian patients' by Krawczyk et al.

We read with interest the paper of Krawczyck et al. reporting the prevalence of rare/uncommon EGFR gene mutations in nonsmall-cell lung cancer (NSCLC), in a retrospective cohort of 3856 Polish Caucasian patients [1]. As in France, a lot of platforms for molecular analysis of cancers have developed alternative molecular targeted analyses to nontargeted direct sequencing, for only the two most common EGFR mutations (exon 19 deletions, and L858R exon 21 mutation) or for a limited panel of EGFR mutations. Although the next-generation sequencing (NGS) enabling molecular data for the entire tested exons, is actually already used or available in a near future, the question of the predictive value of rare EGFR mutations is likely to remain unresolved. Indeed, since our paper published in 2014 [2], predictive value of uncommon EGFR mutations in routine analysis has rarely been reported in therapeutic trials, excepted recently for afatinib in a pooled analysis of prospective trials [3].

Uncommon EGFR mutations prevalence is ~10% of the total EGFR mutations in a nationwide cohort of 10 117 nonselected Caucasian patients with locally advanced or metastatic NSCLC with 95% of nonsquamous tumors tested [2]. This prevalence has recently been confirmed by the results of the IFCT-Biomarqueurs France project concerning 18 679 Caucasian NSCLC patients tested in 1 year. In this cohort, 1786 mutated EGFR cases have been identified including 205 (11.4%) rare EGFR mutations and 163 (8%) resistance EGFR mutations (exon 20 insertions and T790M muation) for which predictive data will soon be available [4].

Future molecular epidemiological studies will have: (i) to precise the molecular techniques used for EGFR mutations detection in order to be exhaustive or not; (ii) to use the same nomenclature and the same definition of uncommon/rare/complex EGFR mutations between centers; (iii) to precise the characteristics of tested population (histological type, stages, …). In France, due to the lack of predictive value of EGFR mutation in squamous cell carcinoma, the guidelines are to routinely test locally advanced or metastatic nonsquamous cell lung cancers [5]; (iv) to precise the predictive value of such uncommon EGFR mutations which is the major point to discuss for first-line option, EGFR-tyrosine kinase inhibitors (EGFR-TKI) or chemotherapy. EGFR-TKI did not provide clinical benefit to patients harboring distal exon 20 insertions (>A767) and de novo T790M noncomplex mutations. In contrast, mutations in EGFR exon 18 (G719X, E709X) more frequent in smokers, mutations in exon 20 (S768I) or exon 21 (L861Q) as well as complex EGFR mutations depending on the associated mutation, especially common mutations, could be sensitive to EGFR-TKIs [2, 4]. Early clinical revaluation should be considered for patients with uncommon EGFR mutations treated by EGFR-TKIs. Due to the small number of cases with EGFR uncommon mutations, a global registry could be helpful for these particular patients who must be considered case par case.

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disclosure

The authors have declared no conflicts of interest.

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