

Checkpoint inhibitors in metastatic epidermal growth factor receptor-mutated non-small cell lung cancer patients: where we treating the wrong cancer?

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Tyrosine kinase inhibitors (TKIs) is the best treatment choice for patients with epidermal growth factor receptor mutation (EGFR) (1). However; acquired resistance is observed after 10–13 months and therefore these patients have to be investigated firstly for the mutation T790M. This investigation is currently proposed to be performed with re-biopsy in a site with disease progression (2,3). In the case where re-biopsy is not possible then liquid biopsy is proposed (4). In the case of T790M then third generation TKIs are used (5). A serious issue that treating physicians have to take under serious consideration is the possible transformation of an adenocarcinoma with EGFR positive mutation to small cell lung cancer (SCLC) (6). This is also another reason why we should choose re-biopsy instead of liquid biopsy. Tissue from a mass or lymph node with imaging findings (CT-Thorax/PET-CT) with evidence of disease relapse might reveal a transformation from adenocarcinoma to SCLC. This kind of transformation has also been observed with adenocarcinoma harboring anaplastic lymphoma kinase mutation (ALK) to SCLC (7). It has also been observed that in the same patient with adenocarcinoma harboring EGFR mutation after TKI treatment re-biopsy revealed that several hepatic metastasis and thoracic lymphnodes were transformed to SCLC, while the primary site remained

adenocarcinoma (8). Transformation to squamous cell carcinoma has been also observed in EGFR positive patients even without TKI administration (9). Moreover; it has been previously observed the case where a patient with T790M mutation receiving osimertinib was transformed to SCLC (10). In the case where disease relapse in these patients cannot be treated with a TKI, then the novel checkpoint inhibitors nivolumab and pembrolizumab could be administered as second line (11). Pembrolizumab has been recently approved as first line treatment in the case where programmed death-ligand 1 (PD-L1) expression is >50% (12). However; for now in the case where patients have both EGFR positive mutation and PD-L1>50% treatment with TKIs is preferred (13). Currently data are conflicting regarding these patients and most of our knowledge is based on murine models (14). It has been observed that even the different exon mutation or EGFR wild type plays a role in the disease response with checkpoint inhibitors after TKI administration (15-17). Different response occurs possibly because of the different factors involved in the acquired resistance. Moreover; currently we are focusing on the expression of the PD-L1 in order to administer checkpoint inhibitors, however; we should consider other factors in EGFR positive mutation patients. There is definitely different immunogenicity for

this subgroup of patients and therefore we should focus on investigating an additional marker before administering checkpoint inhibitors, or we could make additional studies investigating the different response to checkpoint inhibitors based on the different exon mutation or wild-type mutation. Another issue is the different percentage of PD-L1 expression, a stratification would also be useful. We could check the PD-L1 expression of the patients that received checkpoint inhibitors as second lone treatment along after disease relapse in TKI administration with the concept of two groups >50% or <50%. Furthermore; does the administration of osimertinib induce different immunogenicity in comparison to those that received just erlotinib, gefitinib or afatinib and therefore different treatment efficiency for the checkpoint inhibitors. Major issue that is unanswered do we need re-biopsy for the evaluation of PD-L1 expression. Upon diagnosis of adenocarcinoma we investigate EGFR, ALK and PD-L1 expression, what we do not know is if the PD-L1 expression changes during therapy. Does the expression of PD-L1 change throughout the treatment with checkpoint inhibitors and therefore a treatment break is necessary? Re-biopsy should be definitely considered in EGFR patients in a site that the disease response does not correlate with the rest of the imaging findings. In the case of cancer transformation the treatment should change based on the type. Finally, we are expecting results from treatment combinations with TKIS and checkpoint inhibitors after disease progression with TKIS, however; we have to consider the adverse effects of this combination (18,19). Possibly in the future we will have combination of treatments in order to avoid early acquired resistance.

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Footnote

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