1423P Pre-treatment EGFR-T790M subclones in lung adenocarcinoma harboring activating mutation of EGFR: A positive prognostic factor for survival?

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Background: In lung adenocarcinoma, activating mutation of EGFR (aEGFR) and EGFR-T790M can coexist. T790M confers resistance to 1st and 2nd generation TKIs, the standard 1st line treatment. T790M may also be observed at diagnosis (preT790M+) in 0,5-3% cases using standard techniques and up to 30% with highly sensitive ones. FDA and EMA approved osimertinib, a 3rd generation TKI overcoming T790M resistance, for 2nd-line in patients T790M+. Recently FDA approved it for 1st-line of aEGFR+ metastatic disease. Current guidelines make no distinction in aEGFR patients with or without preT790M+. In the osimertinib era it becomes important to detect properly T790M at diagnosis and to define the best strategy for preT790M+. The aim of this study was to find differences in terms of survival and response rate between preT790M+ and wild-type for T790M (WT), detecting T790M with a highly sensitive technique.

Methods: We selected aEGFR+ lung adenocarcinoma who received 1st or 2nd generation TKI in 1st line treatment in our Institution. We reanalyzed the tumor samples of the diagnosis with RainDrop Digital PCR. For statistical analysis we used Kaplan-Meyer method and log-rank test.

Results: We analyzed tumor samples of 28 subjects. At diagnosis, all were wild-type for T790M with standard techniques. With RainDrop Digital PCR, preT790M+ were 28,6% (n = 8). In $\geq$ 2nd lines 50% of preT790M+ and 30% of WT received osimertinib,

according to T790M detection after progression. 1-yr and 2-yr survival were, respectively, 100% and 89% for preT790M+; 68% and 60% for WT. Median OS (mOS) of preT790M+ was not reached at the end of followup and 32.7 months for WT ($p = 0.098$). There were no differences in mOS stratifying by osimertinib use the study population ($p = 0.792$) and preT790M+ subgroup ($p = 1.000$). RR was 87,5% for preT790M+, 60% for WT ($p = 0.241$). Median PFS was 10,4 months for preT790M+, 13.3 months for WT ($p = 0.721$).

Conclusions: Our data, with the limits of the small sample size, show that the coexistence at diagnosis of aEGFR and T790M is not negligible. PreT790M+ tumors could represent a more indolent disease. Further studies are needed to define the optimal timing for osimertinib in these patients.

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