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MA 07.06

Detection of Mechanisms of Resistance to ALK Inhibitors in Routine Practice: A Retrospective Study



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Background: Treatment of ALK-rearranged Non-Small Cell Lung Cancer (NSCLC) relies on ALK tyrosine kinase inhibitors (TKI). However, efficacy of ALK TKI is limited by the emergence of drug resistance. ALK molecular alterations (amplification or mutation) account for about 40% of mechanisms of resistance to ALK TKI. Even though clinical and fundamental data suggest variability in drug efficacy according to the mechanism of resistance, these mutations are rarely investigated in routine practice. While targeted next-generation sequencing (t-NGS) is increasingly used for detecting molecular abnormalities, the impact of this tool in routine detection of ALK alterations is unknown. **Method:** We performed a retrospective multicentric study aiming at determining the frequency of ALK alterations using t-NGS in metastatic ALK-rearranged NSCLC patients progressing upon ALK TKI. Clinical, pathological, molecular characteristics, and patients outcome were collected. **Result:** We identified 22 patients with metastatic ALK-rearranged NSCLC who underwent a rebiopsy at progression on first ALK TKI, between January 2012 and May 2017. There were 12 females and 10 males, median age was 55, 18 patients (82%) were never smokers. Crizotinib was the first ALK TKI in 21 patients (95%). 15 patients (68%) received a second-generation ALK inhibitor and 3 patients (14%) received a third generation of ALK inhibitor. t-NGS on rebiopsy was performed in 16 patients. 6 ALK mutations (37.5%) were identified, including 3 G1202R, 1 C1156Y, 1 V1180L and 1 L1196M mutations. An ALK amplification (6%) was detected in a rebiopsy (6%) by FISH, with no concomitant ALK mutation. All ALK mutations were detected in solid biopsy, 2 ALK mutation was also detected in liquid biopsy. Median Overall Survival from first ALK TKI was 797 days (IC 95% 460-1135) and tended to be longer in patients with a known mechanism of resistance (1135 days Vs 543 days p=0.2). **Conclusion:** Targeted NGS is feasible in routine practice for detection of mechanisms of resistance to ALK TKI in ALK-rearranged NSCLC patients and may help selecting the best treatment at progression upon ALK TKI. **Keywords:** NSCLC, EML4/ALK, Resistance, NGS

MA 07.07

Clinical Outcomes and ALK Resistance Mutations in ALK+ Non-Small Cell Lung Cancer According to EML4-ALK Variant



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Background: Advanced ALK+ non-small cell lung cancers (NSCLCs) are effectively treated with ALK tyrosine kinase inhibitors (TKIs). However, clinical outcomes among patients treated with ALK TKIs vary, and the clinical benefit of TKI therapy is limited due to acquired resistance. To date, emerging data suggest that the specific *EML4-ALK* variant may impact clinical outcome, but whether variant is associated with

mechanisms of TKI resistance is unknown. **Method:** We identified 108 advanced ALK+ NSCLC cases with known *ALK* fusion variants. Progression-free survival (PFS) on ALK TKIs and resistance mechanisms were retrospectively evaluated according to *ALK* variant. **Result:** The 108 ALK+ cases consisted of: 42 (39%) *EML4-ALK* v1 (E13;A20), 8 (7.4%) v2 (E20;A20), 45 (41.7%) v3 (E6;A20), 3 (2.8%) v5 (E2;A20), 4 (3.7%) v5' (E18;A20), 1 (0.9%) v7 (E14;A20), and 5 (4.6%) non-*EML4-ALK* variants. Given the small numbers of non-v1/v3 cases, v1 and v3 cases were selected for further analysis. Among the 21 v1 and 25 v3 cases treated with first-line crizotinib, there was no significant difference in PFS (HR = 0.81 [95% CI, 0.42-1.57], p = 0.526). Similarly, there was no difference in PFS on second-generation ALK TKIs among 35 v1 and 35 v3 patients who received ceritinib, alectinib, or brigatinib following first- or later-line crizotinib (HR = 1.32 [95% CI, 0.77-2.26], p = 0.308). Interestingly, among 12 v1 and 17 v3 patients who received the third-generation TKI lorlatinib after failure of a second-generation TKI, v3 was associated with significantly longer PFS than v1 (HR = 0.250 [95% CI, 0.09-0.72], p = 0.006). From our cohort, we identified 11 v3 and 14 v1 post-crizotinib biopsies. No difference was noted in the presence of *ALK* resistance mutations (27% and 21%, respectively; p = 1.000). In contrast, among 30 v3 and 18 v1 post-second generation TKI biopsies, *ALK* resistance mutations were more common among v3 vs v1 cases (66% vs 44%, respectively; p = 0.147). Furthermore, the ALK G1202R solvent front mutation occurred more frequently in v3 vs v1 (47% vs 0%, respectively; p = 0.001). **Conclusion:** Our findings suggest that *EML4-ALK* variants 1 and 3 may not be associated with significantly different PFS outcomes on crizotinib or second-generation ALK TKIs. However, *ALK* resistance mutations, particularly G1202R, occur more frequently in v3 vs v1 post-second generation TKI. Patients with this variant may therefore derive particular benefit from third-generation, pan-inhibitory ALK TKIs. Larger, prospective studies will be needed to confirm these findings. **Keywords:** tyrosine kinase inhibitor (TKI), Resistance, ALK variant

MA 07.08

Clinical Implications of ALK Resistance Mutations: Institutional Experience and Launch of Remote Participation Study



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Background: ALK resistance mutations are detected in 30-50% of the patients with ALK-positive non-small cell lung cancer (NSCLC) and resistance to ALK tyrosine kinase inhibitors (TKIs). Preliminary data suggests that TKI-resistant patients benefit from further ALK inhibition based on the specific resistant mutations, but clinical data are limited. **Method:** Patients with ALK-positive NSCLC were identified from our institutional database with IRB approval. Tumor specimens from patients with TKI-resistance were analyzed using next-generation sequencing (NGS). We aimed to study the relationship between specific ALK-resistant mutations, patient characteristics and clinical outcomes. **Result:** Among 82 ALK-positive NSCLC patients, we identified 29 cases with advanced disease, TKI resistance, and specimens available for NGS. Twenty-two specimens from 19 patients were adequate for genomic analyses. Patients received a median of 4 lines of treatment for advanced disease including a median of 2 ALK TKIs, with a median overall survival (OS) of 3.3 years. In 9 of 22 specimens, crizotinib was the only TKI received. Ten specimens (45.5%) showed an ALK resistance mutation: one G1128A, one L1152R, four I1171N/T, two F1174V and two G1202R. ALK-resistance mutations were more common with *EML4-ALK* variant 3 (4/5) than variant 1 (1/5). Three cases with sequential biopsies showed features of tumor evolution, such as a compound mutation (I1171N + C1156Y) or a mutational change