Mechanisms of primary and secondary resistance to RET inhibitors in patients with RET positive advanced NSCLC.


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BACKGROUND

RET fusions are found in 1-2% of patients (pts) with advanced non-small cell lung cancer (aNSCLC). RET inhibitors (RETI) have shown excellent objective response rates and progression-free survival, but resistance eventually occurs. Molecular mechanisms of resistance are still incompletely characterized.

Aim: To report molecular mechanisms of primary and acquired resistance to RETi

METHODS

Retrospective multi-center study including 96 patients from 24 European centers with:
• Advanced RET-positive NSCLC treated with RETi
• With at least one molecular profile before and/or after RETi treatment by NGS

Primary resistance or early progression (PD): PD occurred within 6 months of therapy with RETi.

Acquired resistance or late PD: pts who stayed on treatment more than 6 months

RESULTS

Characteristics | Overall (N=96) | Early PD (N=24) | Late PD (N=72) | P value
--- | --- | --- | --- | ---
Age (median, range) | 65 (57-72) | 66 (59-73) | 63 (56-72) | p=0.3
Sex - Male | 39% | 39% | 38% | p=0.9
- Female | 61% | 61% | 62% | p=0.9
Smoking - never | 55% | 55% | 57% | p=0.3
- Former - Current | 44% | 45% | 53% | p=0.3
Brain mets | 17% | 4% | 21% | p=0.11
Histology - ADK | 94% | 91% | 95% | p=0.3
Other | 6% | 9% | 5% | p=0.3
PD-L1: < 1% 2-4% ≥ 50% | 41% 31% 28% | 32% 32% 36% | 44% 21% 25% | p=0.5
N r of lines: 1 - 2 - 3 | 22% 40% 38% | 13% 57% 34% | 25% 41% 41% | p=0.2
Treatment: Selpratentinib Pralatrexib Other | 39% 57% 6% | 30% 61% 41% | 56% 41% 3% | p=0.3

No significant difference in terms of demographic characteristics. TP53 co-mutations were found in both groups, without significant difference, while SMARCA4, STK11, NF1, FGFR2 and KRAS G12V mutations were observed only in patients with early PD.

CONCLUSIONS

On progression on RETi may be associated with the presence of selected co-mutations, such as KRAS, SMARCA4. Secondary RET mutations and MET/MYC amplifications were identified after treatment with RETi. More than half of pts had insufficient ctDNA at PD, making tissue biopsy essential to identify resistance mechanisms.

Acquired alterations and treatment duration

N=11 patients with sequential biopsies under RETi

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