Smoking-Related Genomic Mutation Patterns in Patients With Small Cell Lung Cancer Treated in the ASTRUM-005 Study

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Background

- Transversion mutations (interchanges between purine and pyrimidine) occur predominately in tobacco smokers, whereas transition mutations (interchanges within purine or pyrimidine) are more frequent in non-smokers in smoking-associated cancers.[1]
- In non-small cell lung cancer (NSCLC), several studies have consistently drawn an association between tobacco-smoking history and genetic alterations in cancer-related pathways.[1,2]
- Although small cell lung cancer (SCLC) is strongly associated with tobacco smoking, only a few comparison studies on tobacco-smoking–related mutation signatures were performed with inconsistent results due to the lack of non-smokers in SCLC cohorts.[3,4]
- Here, we report the results of mutation signature analyses for patients with SCLC in the ASTRUM-005 trial and the relation of their tobacco-smoking history.

Methods

- ASTRUM-005 was a randomized, double-blind, placebo-controlled, global, phase 3 trial in patients with extensive-stage SCLC (**Figure 1**).

Figure 1. Study design

Smoking signature analysis

- Genomic mutations in 302 patients with available baseline tumor samples were assessed by the Med1CDx panel, which included exon regions of 601 genes.
- Two bioinformatic methods, the transversion/transition ratio (TTR) method and the Catalogue of Somatic Mutations in Cancer (COSMIC) Signature 4 method, were applied to analyze tobacco-smoking–related signature.
- For the TTR method:
  - An R Bioconductor package, Maftools, was used to calculate the fraction of transversion and transition in each sample. TTR value was then defined as the transversion fraction divided by the transition fraction in each sample.[3,5]
  - Specifically, Maftools classified single nucleotide variants (SNVs) into 6 different transition and transversion events (C>A:G>T, C>G:G>C, C>T:G>A, T>A:A>T, T>C:A>G, T>G:A>C).
  - Synonymous SNVs were included in these analyses.
- For the Signature 4 method:
  - Mutational signatures were extracted and the contributions of tobacco-smoking–related signatures (Signature 4), annotated by the COSMIC, from the genomic mutation panels of each patient were estimated.[6]
  - R package "deconstructSigs" was used to calculate the contribution of the mutation.[7]
  - Both methods were validated on targeted panel sequencing from a published NSCLC data set. Both methods were able to distinguish smokers from non-smokers in NSCLC.[8]

Statistical analysis

- For progression-free survival (PFS) and overall survival (OS), the median was calculated from product-limit (Kaplan–Meier) estimates, while n was the number of patients in each subgroup category. The hazard ratio (HR) and its 95% confidence interval (CI) were estimated using an unstratified Cox proportional hazards model; Efron's method was used to handle ties.
- For the analyses of genomic-based smoking signatures, the Wilcoxon test was used to calculate the difference among patients with different smoking histories. The clinical data cutoff date was June 13, 2022.

Figure 2. Mutation differences by smoking history

OR, odds ratio. *$P < 0.05$; **$P < 0.01$.
OR < 1 means more mutants are observed in never smokers.
OR > 1 means more mutants are observed in ever smokers.

Figure 5. Mutation differences by high/low TTR

OR, odds ratio. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
OR < 1 means more mutants are observed in the low TTR group.
OR > 1 means more mutants are observed in the high TTR group.