



Baseline Gut Microbiome and Metabolomic Signatures Associated With Durable Response to First-Line EGFR-TKIs in EGFR-Mutant NSCLC



Presenting Author: Jing-mian Jiao, Dan Zang, Jun Chen*

Correspondence: chenjun_dmu@126.com

INTRODUCTION

Clinical outcomes to first-line third-generation EGFR-TKIs remain heterogeneous in patients with advanced EGFR-mutant NSCLC. The gut microbiome and its metabolites have been implicated in modulating treatment response, but baseline determinants of durable benefit remain unclear. This study evaluated baseline microbiome and metabolomic features associated with durable response in stage IV EGFR-mutant NSCLC..

METHODS

A total of 29 patients were included (R, n=19; NR, n=10). Median PFS differed markedly between groups (24 [22–36] vs 6 [2–8] months). Baseline characteristics, including age (58 vs 59 years), sex distribution, and smoking status, were balanced between responders and non-responders.

RESULTS

Species-level α -diversity analysis demonstrated significantly higher microbial richness and diversity in the R group compared with NR ($P=0.024$), with an overall upward shift in diversity distribution.

Differential abundance analysis at the species level identified enrichment of *Alistipes* sp. HGB5, *Eubacterium* sp. AF22_9, and *Tyzzzeria nexilis* in the NR group compared with R (all $P<0.05$), forming a response-associated microbial cluster within the phylogenetic structure. Metabolomic profiling showed consistently elevated levels of lipid- and bile acid-related metabolites in responders, including chenodeoxycholic acid, testosterone glucuronide, and palmitic acid (all $P<0.05$), with a uniform upward shift and broader distribution across metabolites, demonstrating clear separation from the NR group. Integrative microbiome–metabolome analysis demonstrated that *Tyzzzeria nexilis* was positively associated with chenodeoxycholic acid and palmitic acid, suggesting its role as a central node linking microbial composition to lipid and bile acid metabolic pathways

CONCLUSIONS

Durable response to first-line third-generation EGFR-TKIs is associated with distinct baseline gut microbiome composition and metabolomic profiles in EGFR-mutant NSCLC. Coordinated enrichment of specific microbial taxa and lipid/bile acid-related metabolites, particularly involving *Tyzzzeria nexilis*, suggests a microbiome–metabolome axis linked to sustained therapeutic benefit. These findings support further investigation of baseline microbiome–metabolite features as predictive biomarkers.

RESULTS

