Temporal Gut Microbiome Signatures Associated with Response and Toxicity to Immune Checkpoint Inhibitors in Asian NSCLC

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BACKGROUND

- Gut microbiome have been implicated in modulating response to immune checkpoint inhibitors (ICIs), but the temporal dynamics linking microbial composition and function to treatment efficacy and immune-related adverse events (irAEs) remain poorly defined.
- We sought to characterize time-dependent microbial taxonomic and functional signatures associated with ICI response and toxicity in Asian patients with non-small cell lung cancer (NSCLC).

METHOD

- Stool samples were prospectively collected from 74 NSCLC patients treated with ICIs at baseline, during and/or after immunotherapy treatment,
- Response to ICIs: complete response, partial response, sustained stable disease ≥24weeks.
- Shotgun metagenomic sequencing was performed, with taxonomic and functional annotation using reference-based bioinformatics pipelines (bioBakery).
- 'Multivariate regression models were used to identify microbial taxa and KEGG orthologs (KO) associated with response and irAEs

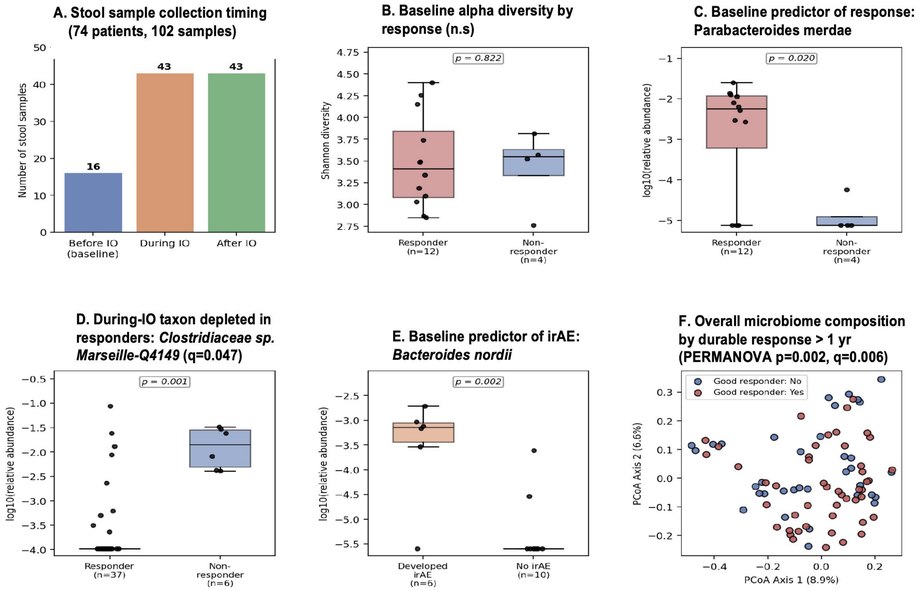
Demographics	N (%) (N=74)
Age (median)	65
Gender Male Female	 60 (81.1%) 14 (18.9%)
Race Chinese Malay Others	 62 (83.8%) 8 (10.8%) 4 (5.4%)
ECOG PS 0-1	 56 (90.5%)
Stage III IV	 15 (20.3%) 57 (77.0%)
Histology Adenocarcinoma Squamous cell carcinoma Others	 59 (79.7%) 7 (9.5%) 8 (10.8%)
ICIs Pembrolizumab Durvalumab Atezolizumab Others	 47 (63.5%) 14 (18.9%) 8 (10.8%) 5 (6.8%)
Response Yes, Durable response of ≥ 1y No	 60 (81.1%), 37 (50%) 14 (18.9%)
IrAEs Yes No	 40 (54.1%) 34 (45.9%)
PD-L1 TPS 50-100	 31 (41.9%)

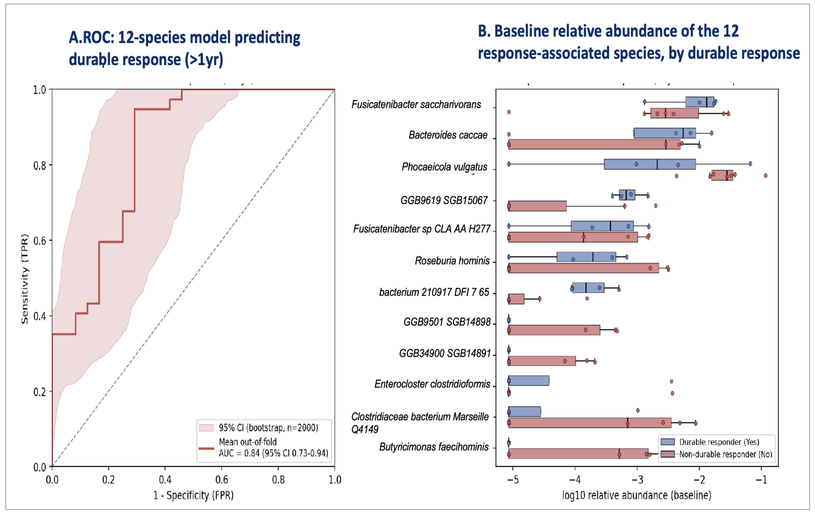
CONCLUSION:

Immunotherapy response and irAEs are associated with distinct, temporally divergent gut microbiome states.
Treatment response correlates with dynamic microbial and functional restraint during immunotherapy, while toxicity appears to be largely predicted by baseline microbiome composition.

These findings support microbiome-informed risk stratification and targeted modulation strategies to optimize immunotherapy outcomes.

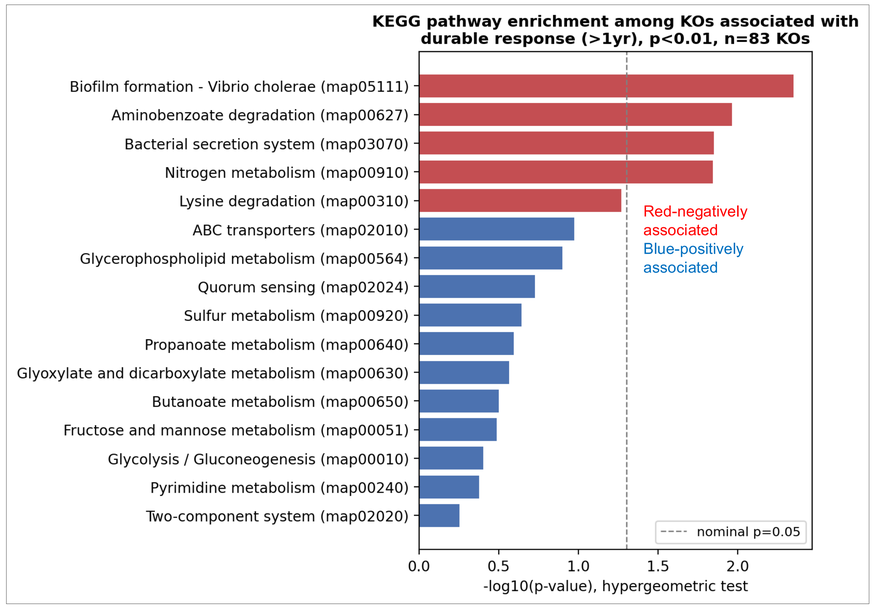
RESULTS





A 12-species baseline signature predicts durable response (>1year) to immunotherapy.

- Using baseline samples, penalized logistic regression model was used to generate an algorithm to predict for durable response (>1yr). Twelve key taxa were identified



- 81(out of 83) genes were ***depleted*** in durable responders--> Bacterial secretion system, biofilm formation, aminobenzoate degradation & nitrogen metabolism were statistically significant for enrichment ($p<0.05$, FDR $q<0.1$). (red)
- 2 (out of 83) genes were ***positively*** associated with durable response and were involved in SCFA (short-chain fatty acids) pathways (blue)

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